Book 6: Treatment Nihilism by the Disuse of PASSIVE IMMUNIZATION in the early treatment of Postexposure and/or the early Viral Infection (during the viremic phase): e.g: COVID-19, RSV, measles (Rubeola)

Charles H. Andrus, M.D., F.A.C.S.
NIH NIAID Case file #12276
March 29, 2025

Over the course of the last five years under NIH NIAID case file number 12276, I have submitted my concerns regarding our treatment of COVID-19, RSV and measles to many within the federal government.[1-6] When one looks at my writings over that time period, they reflect the inherent misdirection of our thinking or lack of a unification of thought rationale with regards to Clinical Immunology. In medical school during my basic science years, I was exposed to the concept of immunology and its applications in medicine at the time. My initiation into the medical profession was at the time of the start of the pandemic of human immunodeficiency virus (HIV), the development in the techniques of DNA sequencing, and the elaboration of DNA by polymerase chain reaction (PCR). Molecular biology concepts were in their infancy compared to that which we know today. Many of the facets of the seemingly divergent aspects of immunology were outwardly and apparently divergent in application and implementation in Clinical Medicine with our *de facto* neophytic comprehension. Clinical (therapeutic) Immunology at the time of my education was foundationally divided into:

> ***Active Immunization*** (**prophylaxis** by vaccination) is the provision of exogenous antigens to the individual to promote the body to produce acutely, specific, endogenous immunoglobulins against the presented antigens with, over roughly 2 week course, the production of IgGs with the resultant long-term development of plasma cells that retain the memory of the exogenous antigens for years to come. As the development of plasma memory cells are long-term, vaccination (possibly with boosters) can be for life, e.g.: smallpox (and now monkey pox), DPT, MMR, polio, RSV, chickenpox, hepatitis B vaccines, etc.
>
> Versus
>
> ***Passive Immunization*** (**treatment** by convalescent plasma and sera--and today monoclonal antibodies, etc.) is the provision of exogenous antibodies to the individual to address acutely and immediately with exogenous IgGs to specific antigens of infections, toxins, and envenomations in the individual. While accomplishing an immediate treatment during the early phase (viremia) of the disease, these administered exogenous IgGs will have diminishing effectiveness in the individual's serum over about 2 months as the half-life of these IgGs are about 20-30 days, e.g.: Pasteur's rabies "vaccine", hyperTet, RhoGam, IVIGs, monoclonal antibodies and antibody cocktails, gammaglobulins like GamaSTAN® S/D in regards to measles, anti-snake venoms, etc.

Thus, while ***Active Immunization*** in the individual is relatively long-lasting and protective in the immunocompetent individual, ***Passive Immunization*** in unvaccinated, under-vaccinated, and immunologically-incompetent individuals is a relatively short-lived but can be life-saving treatment for exposed or infected individuals. The euphemistic confusion in Medicine today, though, promotes vaccination (*active immunization*) as a treatment--which it is not; and, the only always available, continuely updating specific *passive immunological* source is some form of Convalescent Plasma from a recovered, previously-infected individual. Throughout this *Book 6: Treatment Nihilism by the Disuse of PASSIVE IMMUNIZATION in the early treatment of postexposure and/or the Viral Infection (during the initial viremic phase) are analyzed: e.g: COVID-19, RSV, measles (Rubeola)*, the resultant misdirections and failures with regards to COVID-19, RSV, and the recent outbreaks of measles (*Rubeola*).

1. **Statistically,** in regards to COVID-19, SARS-CoV-2 and published RCT trials with mortality as their primary end-point, all are underpowered statistically over the last five years due to the substantial, upwardly increasing mortality rate (~0.5% per year) after age 49 as derived from the published CDC data from 2020-early 2021 that were collected and reported prior to or just at the initiation of the COVID-19 Vaccinations to the U.S.A. public.
   https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge:

   50 – 90+ years of age: Mortality rate (y) = 0.0052 (x) – 0.1305 $r^2 = 0.99$

   The Graphs used in the derivation of this aforementioned equation can be found on page 341 in this Book 6 in: 0.9 Attachment VIII_Pg 24_Graph IV from Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals

   With such a dramatic increase in mortality rate for COVID-19 per year, a large number of subjects in each age subgroup are necessary to appropriately compare the effectiveness of a therapy in promoting survival.[7-9]

2. **March 29, 2025**: On Friday evening, 3/28/2025, it was announced that Peter Marks, M.D., PhD resigned from the FDA as the "top vaccine scientist." This statement of his being the "top vaccine scientist" was *palteringly* incorrect as Dr. Marks was the **Director of the FDA's Center for Biologics Evaluation and Research (CBER)** which meant that he had overview responsibilities regarding all Biologics including those of *Active Immunization* (vaccines) and *Passive Immunization* (all exogenous immunoglobulins used to treat viruses and bacteria, toxins, and envenomations).

Please note: My Letter (pages 11-74) to HHS Secretary Robert F. Kennedy was mailed on 03/22/2025 via USPS Priority Mail with tracking # 9405530109355121386196. It was reported on 3/29/2025, in USPS tracking that it has yet to be delivered to Secretary Kennedy as is documented by the USPS tracking below. Such documentation implies that my recommendation that Secretary Kennedy speak with Dr. Marks (page 19) will arrive after he resigned or was fired. It is likely, though, that Secretary Kennedy was given a copy of my

letter prior to Dr. Marks separation from the position of Director of the FDA's Center for Biologics Evaluation and Research (CBER) as I had attached a copy of my letter to Secretary Kennedy to an e-mail sent to Acting Surgeon General Denis Hinton, US PHS Rear Admiral, MS, RN, FAAN that was dated and timed: Monday, March 24, 2025 at 03:55 PM CDT **(page 345) which was thus delivered to the Office of the Surgeon General to the e-mail address:** surgeongeneral@hhs.gov **four days before Dr. Marks' resignation or firing as the Director of CBER.**

THIS IS EXTRMEMLY IMPORTANT as the *Passive Immunity* agent, GamaSTAN® S/D, a gamma globulin agent that was approved by the FDA in 1944; and GamaSTAN® S/D is still approved today in the treatment within six days of exposure to Hepatitis A and measles (Rubeola). In all the present discussions in the media today, nowhere is it stated that all those exposed to measles who are unvaccinated, under-vaccinated, or immunocompromised should be administered GamaSTAN® S/D or IVIG / Convalescent Plasma specific for measles (Rubeola).

THIS IS HOW THE PRESENT MEASLES OUTBREAKS SHOULD BE TREATED!

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Retired, Professor of Surgery, Saint Louis University School of Medicine
Retired, Physician and Surgeon, Veterans Health Administration,
U.S. Department of Veterans Affairs
NIH NIAID case file #12276
Home phone: 314-455-9482

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REFERENCES:

1. **BOOK 1 Dr Mr President.. COVID 19 And Where We Went Wrong 2023 02 02**

By Charles H. Andrus, M.D., F.A.C.S.

https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02

Publication date: 2023-09-12
Topics: COVID-19, Dr Mr President, Wrong
Collection. opensource
Item Size: 973.4M

This is a copy of Book 1: Dear Mr. President...COVID-19 and Where We Wrong first submitted to agencies of the DHHS, the DVA, and the President of the United States in September 2022. It has been edited over the last year but is still in draft form. What is more, the submission to the Internet Archive is for NO personal financial gain. As a former VHA physician and surgeon of the U.S. Department of Veterans Affairs, it is (1) my duty as a former federal physician and (2)

mandate to the oath I swore professing Primum non Nocere, that today, I submit this to the American people as a purely educational contribution that should be debated, analyzed, and appropriately acted upon by U.S. Medicine, the FDA, the NIH, the NIAID, the VA, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.

2. BOOK 2 0 2023 09 11 Scan VA RSSO Case 286816 Letter Arrived Feb 13 2023

By Charles H Andrus, M.D., F.A.C.S.

https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/0%202023-09-11%20scan%20VA%20RSSO%20Case%20286816%20letter%20arrived%20Feb%2013%202023/

Publication date: 2023-09-11
Topics: VA RSSO Case 286816, NIH NIAID Case# 12276
Collection. opensource
Item Size: 53.8M

This is the final cover letter from the VA Workforce Management & Consulting (WMC), Retirement Shared Service Office (RSSO), VA RSSO Case #286816 received by Dr. Andrus on Feb 13, 2023, with the 18 lbs of documentation submitted by Dr. Andrus on January 30, 2023 per the request of the VA RSSO. The fourth paragraph inappropriately closed the door on the recalculated back pay of ~$82,000 owed to Dr. Andrus and revision of his monthly pension by: "...after speaking with leadership, it was determined to return the documents you have mailed in as they are not pertinent to your salary discrepancy or the retirement."

3. Book 3 Abridged Dear Mr President... To Care For Him Who Shall Have Borne The Battle 2024 02 29

By Charles H. Andrus, M.D., F.A.C.S.

https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-the-battle-2024-02-29

Publication date: 2024-02-29
Topics: IL-372, PATH, Physicians at Teaching Hospitals, Veterans Health Adminstration, Resident Supervision, to care for him who shall have borne the battle
Collection: opensource
Item Size: 1.2G

This is an abridged version of the yet to be uploaded Dear Mr. President...To Care for Him Who Shall Have Borne the Battle...A. Lincoln which is a composite (of > 3500 pages) of this abridged version of Book 3--A confirmatory chronological compendium of primary sources and resultant correspondence between Dr. Andrus and: (1) the U.S. Department of Veterans Affairs [VA OIG 2000 HL-0347, 9HL-015, U.S. DVAORM/EEO 200k-1886; U.S. EEOC 03A20075, 210-A2-6164X, 210-A3-6145X, etc.], (2) the U.S. Merit Systems Protection Board, (3) the EEOC, (4) the U.S. Court of Appeals for the Federal Circuit, docket case #03-3162, (5) the Veterans Affairs Committee of the U.S. House of Representatives, (6) the U.S. Office of Special Counsel [MA-00-1107, DI-00-1147], (7) the U.S. Department of Justice, (8) The White House, (9) Academic and Research Medical Organizations and Medical Societies (e.g.: the CDC, AMA, ACS, NIH NIAID case #12276 between 2020 – the present, etc.) and the staffs of the NEJM, JAMA, American Journal of Surgery, etc., and other academic and research entities of American Medicine.

The central issue of this book covering over 5 decades is allegations of the de facto denial of care, the de facto dereliction to duty, and the de facto disregard of patients' rights by some Teaching Physicians and Surgeons in the condoning of Ghost Surgery for a halfcentury.

(Ghost Surgery: Attending Surgeon supervising but not physically being present during the performance of operations, procedures, and encounters by physicians-in-training [residents].)
This book documents the misapplications by some of the Rules of Attending Surgeon Supervision as mandated in the private and public section under Intermediary Letter 372 (IL-372) of the Social Security Administration and in the Veterans Health Administration under VHA Handbook 1400.1.
Much of the subsequent correspondence is permeated with legal obfuscation and chronic denial.

Submitted respectfully as is my duty as a retired Physician and Surgeon, Veterans Health Administration, U.S. Department of Veterans Affairs,

Charles H. Andrus, M.D., F.A.C.S.
former Chief, Surgical Services, Edward Hines, Jr. VAH, Maywood, IL (tertiary Chicago VA hospital and first VAH of the University/VA affiliation in 1946, PL 79-293), Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (1996 - 2002)
former Professor and Vice-chairman, Department of Surgery, Loyola University School of Medicine (1996- 2001)
retired Attending Surgeon (and for most of the time, Chief, Unit II General Surgery--Saint Louis University GS division), John Cochran (St. Louis) VAMC, Veterans Health Administration, U.S. Department of Veterans Affairs (1986 - 1996) and (2016 - 2022)
retired Professor and Surgeon, Department of Surgery, Saint Louis University School of Medicine (2006 - 2022); Medical Student: 1975 - 1979, Pediatric Resident: 1979 - 1981, General Surgery Resident: 1981 - 1986, faculty: 1986 - 1996, 2006 - 2022.

VA IG document adjunct to Book 2 and Book 3: 06.3005 1999 11 22 Hines VAH CAP 99 00173 18 Copy

By: Charles H. Andrus, M.D., F.A.C.S. uploaded as this VA OIG report was published for PUBLIC RELEASE, by the U.S. Department of Veterans Affairs, Office of Inspector General on November 22, 1999
https://archive.org/details/06.3005-1999-11-22-hines-vah-cap-99-00173-18-copy/mode/1up

Publication date: 1999-11-22
Topics: U.S. Department of Veterans Affairs, Office of Inspector General, CAP Review, Edward Hines, Jr. VA Hospital, Report No. 99-00173-18, November 22, 1999, https://www.va.gov/oig/pubs/99-00173-18.pdf
Collection: opensource
Item Size: 41.5M

06 1999-11-12 VA OIG report Hines VAH CAP 99-00173

The VA OIG website for the Hines VAH CAP 99-00173-18 has been removed from the VA OIG Website URL: https://www.va.gov/oig/pubs/99-00173-18.pdf which today yields: “Sorry, we can’t find that page”; and this VA OIG Website URL was never uploaded to the Internet Archive over the last 25 years. Thus, on 3/2/2024, I uploaded in a .pdf format a scanned copy of the complete VA OIG report No. 99-00173-18 of November 22, 1999, signed off by Richard J. Griffin, DVA Inspector General, which was 48 pages in length: title page, i-v, 1-42. This scanned copy is contained in its entirety in Chapter 6 of the—as yet, not uploaded-- unabridged Book 3, pages 192-259: 06.3005 1999-11-22_Hines_VAH_CAP_99-00173-18.pdf.
In October/November 1999, roughly 4 weeks prior to the publication of this report by the VA OIG, a young man from the regional IG office on the Hines VAH grounds presented to my Hines VAH office on the fifth floor of Building 200 and asked if I had any documentation of OR resident supervision at the Hines VAH. I, immediately, provided him with a 3 .” diskette which contained the latest monthly report on resident supervision by surgical specialty never realizing that the VA OIG would publish it. It consisted of: A monthly cover letter on Attending Surgeon supervisory levels of residents and an Excel data base entitled Surgery Resident Supervision in OR—FY 99 (the last 17 pages of APPENDIX IV, pages 43-61 of 99-00173-18). (An abridged version of this report can be found on pages 277-283 of Book 3: https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-the-battle-2024-02-29/ . While the title page states VA OIG report No. 99-00173-18 was FULLY-REDACTED, the VA OIG did not redact my name from the cover letter as I was one of the two named signatories on page 44 of the report. (This VA OIG official

report confirms I existed as the Chief of Surgery, Edward Hines, Jr. VA Hospital, Hines, IL on October 14, 1999, which contradicts the official search of the U.S. National Archives for the existence of my Official Personnel File (OPF) from 1982 to 2002 as is documented on page 533 of Book 3 https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-thebattle-2024-02-29/ .)
In the letter on page 1 of Book 2: Andrus CH: 0 2023 09 11 Scan VA RSSO Case 286816 Letter Arrived Feb 13 2023. Internet Archive, uploaded: 2023-09-11. https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/0%202023-09-11%20scan%20VA%20RSSO%20Case%20286816%20letter%20arrived%20Feb%2013%202023/ it is stated by the RSSO official: "…In addition, after speaking with leadership, it was determined to return the documents you have mailed in as they are not pertinent to your salary discrepancy or the retirement."
When I resigned from the VHA in January 2002, my Grade and Step was 15-10. When I returned to the VHA in August 2016, I was designated by the VHA as a Physician and Surgeon as a 15-07, a de facto demotion, as there reportedly was no confirmation of my 18 years of service in the VHA from 1982-2002. As is documented on page 4 of 3 Appendix C VA Commendations Andrus 2023-01-29 https://archive.org/details/0-2023-09-11-scanva-rsso-case-286816-letter-arrived-feb-13-2023/3%20Appendix%20C%20VA%20Commendations%20Andrus%202023-01-28/page/n3/mode/1up , I retired with 25 years of service which under Title 38, U.S.C. Sec. 7431, qualified me to be the rank of Grade 15 Step 13 (instead of Grade 15 Step 10).
Res ipsa loquitur: I should have a retirement rank of Grade/Step of 15-13, my calculated outstanding back pay is ~$82,000, and my retirement pension should be recalculated by the RSSO of the DVA for the last 6 years of my VHA service from 2016 – 2022 as my Step and Grade should have been from 15-10 to a 15-13 (Not 15-7 to 15 – 10).
Respectfully,
Charles Andrus, M.D., F.A.C.S.

4. BOOK 4 Biden Response To The Summary Of Book 1 COVID 19 And Where We Went Wrong

By Charles H. Andrus, M.D., F.A.C.S.
https://archive.org/details/book-4-biden-response-to-the-summary-of-book-1-covid-19-andwhere-we-went-wrong
Publication date:
2024-02-05
Usage: Public Domain Mark 1.0
Topics: COVID-19, Active Immunization, Passive Immunization, antivirals, misinformation, obfuscation, FDA, NIH, NIAID, CDC, VHA, The White House
Collection: opensource
Item Size: 650.0M

On July 7, 2023, President Joseph Biden replied to the included summary submission of Book 1: Dear Mr. President: COVID-19 and Where We Went Wrong. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02 NIH NIAID Case #12276. Book 1 is 1266 pages documenting correspondence with the NIAID, the FDA, the VA, and The White House over 3 years concerning the clinical care of patients newly infected with COVID-19. All the documentation that has been submitted to the NIH NIAID Case #12276 (Book 1 is an abridged documentation) is available through the Freedom of Information Act Officer of the NIAID. The submissions to the NIAID and FDA in detail outlined the pathophysiology of coronavirus SARS-CoV-2; the difference between Active Immunization (vaccination for PROPHYLAXIS to stimulate endogenous immunoglobulins) vs Passive Immunization in the TREATMENT of acute COVID-19 [within 72 - 120 hours of diagnosis] through the administration of exogenous immunoglobulins, e.g.: Convalescent Plasma, Monoclonal Antibodies, and Monoclonal Antibody cocktails, etc.); describe extreme misinformation and obfuscation by the NIH, NIAID, FDA, etc.; describe in-depth the inappropriate late timing of administration of immunoglobulins and antivirals (>120 hours from diagnosis of acute infection); and the cover-up by governmental, academic, etc. entities by

electronic overwriting, URL site relabeling/renaming, and website removal; officials, medical researchers, academics, and clinicians, and agencies advancing incorrect or misleading medical statistics and theories that were associated with and were possibly contributory to >1,000,000 reported deaths from COVID-19 in the U.S.A. from March 2020 to the present. -- Charles H. Andrus, M.D., F.A.C.S.

0.4 BOOK 4 Biden Response To The Summary Of Book 1 COVID 19 And Where We Went Wrong 2nd Attemp

By: Charles Andrus, M.D., F.A.C.S.

https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-wentwrong-
2nd-attemp

Publication date: 2024-03-05
Topics: President Biden, 7/7/2023, COVID-19, VA
Collection: opensource
Item Size: 652.9M

On July 7, 2023, President Joseph Biden replied to the included summary submission of Book 1: Dear Mr. President: COVID-19 and Where We Went Wrong. https://archive.org/details/book-1-dr-mrpresident..-covid-19-and-where-we-went-wrong-2023-02-02 NIH NIAID Case #12276. Book 1 is 1266 pages documenting correspondence with the NIAID, the FDA, the VA, and The White House over 3 years concerning the clinical care of patients newly infected with COVID-19. All the documentation that has been submitted to the NIH NIAID Case #12276 (Book 1 is an abridged documentation) is available through the Freedom of Information Act Officer of the NIAID. The submissions to the NIAID and FDA in detail outlined the pathophysiology of coronavirus SARS-CoV-2; the difference between Active Immunization (vaccination for PROPHYLAXIS to stimulate endogenous immunoglobulins) vs Passive Immunization in the TREATMENT of acute COVID-19 [within 72 - 120 hours of diagnosis] through the administration of exogenous immunoglobulins, e.g.: Convalescent Plasma, Monoclonal Antibodies, and Monoclonal Antibody cocktails, etc.); describe extreme misinformation and obfuscation by the NIH, NIAID, FDA, etc.; describe indepth the inappropriate late timing of administration of immunoglobulins and antivirals (>120 hours from diagnosis of acute infection); and the cover-up by governmental, academic, etc. entities by electronic overwriting, URL site relabeling/renaming, and website removal; officials, medical researchers, academics, and clinicians, and agencies advancing incorrect or misleading medical statistics and theories that were associated with and were possibly contributory to >1,000,000 reported deaths from COVID-19 in the U.S.A. from March 2020 to the present. -- Charles H. Andrus, M.D., F.A.C.S.]

5. Book 5: Summary to President Biden 1-18-2025.

Book 5 will be uploaded to the Internet Archive, and can be found by a GOOGLE search for: ***Internet Archive Advanced Search*** *and in Field 1 (Any Field: contains):* ***VA****, and in Field 3 (Creator: contains)* ***Charles Andrus***

6. **Book 6: Treatment Nihilism by the Disuse of PASSIVE IMMUNIZATION in the early treatment of postexposure and/or the early Viral Infection: e.g: COVID-19, RSV, measles (Rubeola).**
The present book 6 will be uploaded to the Internet Archive on March 28, 2025, and can be found by a GOOGLE search for: ***Internet Archive Advanced Search*** *and in Field 1 (Any Field: contains):* ***VA****, and in Field 3 (Creator: contains)* ***Charles Andrus***

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A.M.D.G.

150 Emerald Green Court
St. Louis, MO. 63141
Home: 314-455-9482

March 21, 2025 **NIH NIAID Case #12276**

The Honorable Robert F. Kennedy, Jr.
Secretary, U.S. Department of Health and Human Services (HHS)
Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201
202-690-7000
Fax 202-690-7203

RE: **Immunizations: Passive Immunity / *Treatment* vs. Active Immunity / Prophylaxis** (vaccines) and the indications of ***Passive Immunization***, treating all, who have been exposed to Measles (Rubeola) by infected individuals and are unvaccinated, under-vaccinated, and immunosuppressed with regards to Measles (Rubeola) with post-exposure prophylaxis, e.g. GamaSTAN® S/D IM or Intravenous IgG (IVIG) with titers of anti-measles antibodies

Dear Secretary Kennedy:

The agencies of the U.S. Department of Health and Human Services (HHS): the NIH, the NIAID, the CDC, the FDA, and the US PHS and the American public are faced with ongoing and potentially spreading measles (Rubeola) outbreaks/localized epidemics. Measles[1-6] which is a highly-contagious, respiratory-transmitted viral disease was rampant when you and I were in grammar school—in fact, it is assumed today that anyone born before 1957 is immune:

> Measles is very contagious. It spreads through the air when an infected person coughs or sneezes. You can get measles just by being in a room where a person with measles has been. This can happen even up to 2 hours after that person has left.[2]

On March 7, 2025, the CDC reported 222 cases across twelve jurisdictions[7]: Alaska, California, Florida, Georgia, Kentucky, New Jersey, New Mexico, New York City, Pennsylvania, Rhode Island, Texas, and Washington.[7] Most cases (208) were concentrated in Texas (198) and New Mexico (10), with the outbreak rapidly expanding in these states. In the following week, in the CDC weekly report regarding "Measles Cases and Outbreaks" of March 14, 2025, the CDC reported 3/4 of the cases were in children: 0 – 19 years of age and ~1/4 were in adults[8]:

> As of March 13, 2025, a total of 301 confirmed* measles cases were reported by 15 jurisdictions: Alaska, California, Florida, Georgia, Kentucky, Maryland, New Jersey, New Mexico, New York City, New York State, Pennsylvania, Rhode Island, Texas, Vermont, and Washington….

U.S. Cases in 2025

Total cases

301
Age
Under 5 years: **103 (34%)**
5-19 years: **126 (42%)**
20+ years: **63 (21%)**
Age unknown: 9 **(3%)**

Vaccination Status
Unvaccinated or Unknown: **95%**
One MMR dose: **3%**
Two MMR doses: **2%**

For all practical purposes, with the development and deployment of the MMR (and now MMR II) vaccine over the past generations, measles (Rubeola), mumps, and rubella (German measles) have become endemic and footnotes in history for the present younger generations today in the U.S.A. due to the mandated vaccination at 12-15 months of age and then with 4-5 years-of-age boosters for all children.[9-14] During the height of the annual epidemics when you and I were children, though, those that contracted measles (Rubeola), were unvaccinated, and some required hospitalization. The prevalence of severe adverse outcomes have not changed in epidemiological recordings of measles cases as reported by the CDC[4] of the HHS:

> **Hospitalization:** "About 1 in 5 unvaccinated people in the U.S. who get measles is hospitalized."
> **Pneumonia:** "As many as 1 out of every 20 children with measles gets pneumonia, the most common cause of death from measles in young children."
> **Encephalitis:** "About 1 child out of every 1,000 who get measles will develop encephalitis (swelling of the brain). This can lead to convulsions and leave the child deaf or with intellectual disability"
> **Death:** "Nearly 1 to 3 of every 1,000 children who become infected with measles will die from respiratory and neurologic complications."
> **Complications during pregnancy:** "If you are pregnant and have not had the MMR vaccine, measle my cause birth prematurely, or have a low-birth-weight baby.
>
> **Long-term complications:**
> **SSPE (subacute sclerosis panencephalitis**) is a very rare, but fatal disease of the central nervous system. It results from a measles virus acquired earlier in life.
>
> > SSPE generally develops 7 to 10 years after a person has measles, even though the person seems to have fully recovered from the illness.
> >
> > Since measles was eliminated in 2000, SSPE is rarely reported in the United States.
> >
> > Among people who contracted measles during the resurgence in the United States in 1989 to 1991, 7 to 11 out of every 100,000 were estimated to be at risk for developing SSPE
> >
> > The risk of developing SSPE may be higher for a person who gets measles before they are 2 years of age.

In deference to ***Active Immunization*** (vaccination of the individual to stimulate endogenous antibodies), since 1944[15-17], ***Passive Immunization*** (administration of exogenous antibodies in the form of gamma globulin, e.g: GamaSTAN, or IVIG with IgG titers of measles antibodies) -- pooled sera or plasma of exogenous IgG from donors who have recovered from the measles--has been administered in the early course of measles disease and in post-exposure prophylaxis (PEP) to diminish severity of illness in all contacts especially all immunosuppressed contacts within 6 days of measles exposure.[18-33,120] The FDA approval continues regarding intramuscular GamaSTAN® S/D as it is officially listed by the FDA as an approved immunoglobulin.[20] In

studies reported over the last twelve years, GamaSTAN and/or IVIG containing measles IgG antibodies in the suppression of measles has been documented to be extremely effective[22,34,35]:

> **Results:** In 63 (96.9%) of 65 infants PEP of 65 infants PEP with IVIG was administered. The parents of two infants declined IVIG PEP. None of the infants with IVIG PEP got measles or symptoms suggestive for measles, but both infants who did not receive PEP were infected. Effectiveness of IVIG PEP was calculated to be 99.3% (CI 95%: 88.7-100%). No serious adverse event of IVIG treatment was observed. The investigation on MV-neutralizing antibody capacity showed a geometric mean titer ranging from 10.0 to 12.7 IU/ml, resulting in a 1.57-2.26-fold higher concentration than postulated as minimum level for immunity.
> [Kohlmaier *et.al.:* Effectiveness and safety of an intravenous immune globulin (IVIG) preparation in post-exposure prophylaxis (PEP) against measles in infants. Front. Pediatric Infectious Diseases 2021 December 01; 9: Article 762793]

> **Results:** A total of 3409 contacts were identified, of which 208 (6.1%), 274 (8.0%), and 318 (9.3%) met the inclusion criteria for analysis of MMR, IG, and any PEP effectiveness, respectively. Of the contacts included, 44 received MMR PEP and 77 received IG PEP. Effectiveness of MMR PEP was 83.4% (95% confidence interval [CI], 34.4%, 95.8%). No contact who received IG PEP developed measles; effectiveness of IG PEP was 100% (approximated 95% CI, 56.2%, 99.8%). Effectiveness of receiving any PEP (MMR or IG) was 92.9% (95% CI, 56.2%, 99.8%).
> [Arciuolo RJ, *et.al.*: Effectiveness of measles vaccination and immune globulin post-exposure prophylaxis in an outbreak setting—New York City, 2013. Clin Infect Dis 2017 Nov 13; 65(11): 1843-1847. https://academic.oup.com/cid/article/65/11/1843/4210618?login=false]

> **Intramuscular immunoglobulin**
> Available evidence and product information was reviewed concerning IMIg, which has previously been recommended by NACI for measles PEP at a dose of 0.25 mL/kg for susceptible pregnant women and infants or 0.5 mL/kg for immunocompromised individuals, or for other susceptible contacts who presented between 72 hours and six days post-exposure. GammaSTAN (10) is the only IMIg preparation in Canada, and it is indicated for use as measles PEP. When effectiveness studies were examined based on the relative anti-measles antibody concentrations in current Ig products, it was apparent that IMIg doses exceeding the CBER Reference Standard with current protein concentrations of 0.442 mL/kg, 0.393 mL/kg or 0.335 mL/kg, would result in 100%, 100% and 83% effectiveness respectively against measles up to two weeks post-injection (9)…
> [Tunis MC, *et al*: Updated NACI recommendations for measles post-exposure prophylaxis. CCDR 2018 September 6; 44(9): 226-230. https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-9-september-6-2018/ccdrv44i09a07-eng.pdf]

Secretary Kennedy, we are in the midst of outbreaks (potentially localized epidemics) of measles throughout the country in unvaccinated and under-vaccinated children and adults and in immune-incompetent individuals regardless of previous vaccination. Despite your personal impression of vaccines, as the Secretary of the Department of Health and Human Services,

(1) you are the administrative face of the U.S. Department of Health and Human Services and all its agencies;

(2) are the visible spokesman regarding the advocacy for public health measures for all people in America by the agencies under your supervision (e.g., FDA, CDC, NIH, NIAID, USPHS, etc); and

(3), most of all, you have a responsibility to expect those agencies under you to advocate and direct the appropriate medical practice of clinical immunology.

In accordance with the present scientific literature, provision of ***Passive Immunization*** (IVIG or GamaSTAN) **TREATMENTs** with subsequent delayed vaccination with MMR-II ~5 months later is the epidemiologically mandated-post-exposure-prophylaxis for all who are NOT completely immune to measles. This should be and is the standard of care within six days of measles exposure of all not-yet-symptomatic and immunosuppressed individuals that are unvaccinated, under-vaccinated, and when the vaccination history is unknown. The latest insert approved by the FDA regarding GamaSTAN® S/D is as follows[26]:

63 Measles (Rubeola)
64 To prevent or modify measles give GamaSTAN S/D in a susceptible person exposed fewer
65 than 6 days previously.(7) A susceptible person is one who has not been vaccinated and has
66 not had measles previously. GamaSTAN S/D may be especially indicated for susceptible
67 household contacts of measles patients, particularly contacts under 1 year of age, for whom
68 the risk of complications is highest.(7) GamaSTAN S/D and measles vaccine should not be
69 given at the same time.(7) If a child is older than 12 months and has received GamaSTAN
70 S/D, he should be given measles vaccine about 3 months later when the measles antibody
71 titer will have disappeared.
72 If a susceptible child exposed to measles is immunocompromised, GamaSTAN S/D should
73 be given immediately.(8)
74 Do not administer measles vaccine or any other live viral vaccine to children who are
75 immunocompromised.

Thus, GamaSTAN®, GamaSTAN® S/D, or IVIG containing anti-measles antibodies should be given to all as a post-exposure prophylaxis who are non-vaccinated individuals, those inadequately vaccinated, and all who, regardless of vaccination status, are immunosuppressed / immunoincompetent (e.g.: all transplant patients, all taking monoclonal antibodies (-ab), other immunotargeted therapies (-ib), antivirals, etc.).[25-33,36-40] Many of the immunologic treatments (e.g.: for cancers, skin disorders, chronic neurologic disorders, collagen vascular diseases, etc.) are at present pervasively advertised daily on television which is *de facto* condoned by the HHS and the FTC.[41-50] Referenced in this letter are some of the supporting documents of the usage of GamaSTAN or other IVIGs directed towards measles (Rubeola) approved by the FDA and written about by the CDC, the NIAID, the USPS, etc. of which are all agencies under your direction.[15-33]

While the present measles outbreaks in this country will probably diminish over a period of time burning out to a low endemic-level of penetrance as the weeks and months go by, administering GamaSTAN®, GamaSTAN® S/D, or IVIG containing anti-measles antibodies as post-exposure prophylaxis (PEP) to every individual who is exposed to a case of measles who is not vaccinated, under-vaccinated, or immunosuppressed is paramount, medically correct, and morally right.[22,34,51-61] The advocacy for such a collective response should be the responsibility of the agencies of the HHS of which you are now the administratively responsible Secretary: e.g.: the FDA, the NIH, the NIAID, the CDC, the US Public Health service, etc. (Please see the referenced public health directives of numerous Public Health Agencies and other medical entities: e.g., the CDC, BC/BS Federal Employee Insurance program, the State of California, the State of New York, the State of Minnesota, the Canadian CDC (CCDC), etc.[34,51-61]). Unfortunately, due to the subliminal, pervasive practices of electronic overwriting, electronic archiving, and electronic sunsetting of URLs, our present knowledge of Clinical Immunology is a hodgepodge of collective bias of which American Medicine, Academic Medicine, and the agencies of the U.S. Department of Health and Human Services should be ashamed![62-71] [Attachments I[62], II[63], III[68], IV[69],V[70],VI[71]]

Much of this information regarding ***Passive Immunization*** has been lost from general medical knowledge today due to the subliminal pervasive practice of non-preservation in a hardcopy

format as was previously done in archiving in university and hospital libraries throughout the country and in Federal Depository Libraries (FDLP), 44 U.S.C. §19 [72], etc. Decreased accessibility of past knowledge in the Federal Government and in our society by electronic overwriting, archiving to functionally-non-discoverable Federal electronic server farms, archiving to non-governmental electronic server farms such as the not-for-profit *Internet Archive*[73-75] only, and **changing, destroying, or electronically sunsetting the URLs of past pertinent documents is the suppression of availability of this information and destruction of the pathways to this fund of knowledge by electronic archiving**[62-71] which, I would allege, are all violations of the intent and the explicitly defined prohibitions of the Sarbanes-Oxley Act of 2002, 18 U.S.C. 1512(c)(1)[76-78]:

> The Sarbanes-Oxley Act of 2002 imposes criminal liability on anyone who corruptly "alters, destroys, mutilates, or conceals a record, document, or other object, or attempts to do so, with the intent to impair the object's integrity or availability for use in an official proceeding." 18 U.S.C. 1512(c)(1)

The most flagrant example of such information misdirection and thus *de facto* destruction of access to the information is that of the *NIH COVID-19 Treatment Guidelines*.[79-80] While there were 72 iterations over 4 years of the *NIH COVID-19 Treatment Guidelines* and at the bottom of the face-sheet of the final iteration is stated:

> NIH
> www.covid19treatmentguidelines.nih.gov
> An official website of the National Institutes of Health

after August 17, 2024, the URL listed above was removed from the *Internet* and thus non-discoverable by standard search engines like GOOGLE. All iterations of the NIH COVID-19 Treatment Guidelines[79-80] are only locatable through the search of the *Internet Archive* [73-75] (Wayback Machine). The *Internet Archive* is physically located at 300 Funston Avenue, San Francisco, CA--a not-for-profit, non-U.S. Government website data base server farm that is and has wrongfully become the only fallback archive for much of the NIH, FDA, etc. documentation in the ongoing archiving of policies and directives. **IN SHORT, the U.S. Department of Health and Human Services (HHS) and all its subordinate agencies are in violation of the Sarnes-Oxley Act of 2002** [76-78] through **changing, destroying, or electronically sunsetting the URLs of past pertinent documents is the suppression of availability of this information and destruction of the pathways to this fund of knowledge by electronic archiving**[62-71]**; and you, as the Secretary of the HHS, are the administratively/legally responsible party before the U.S. Congress and the American people.**

The pervasiveness of the electronic practice of:

> **changing, destroying, or electronically sunsetting the URLs of past pertinent documents is the suppression of availability of this information and destruction of the pathways to this fund of knowledge by electronic archiving**[62-71]

and is directly related to the greater than a million deaths in the first year of the American epidemic from COVID-19 because of the withholding of exogenous immunoglobulins (***Passive Immunization***) or the administration preferentially at the wrong time at greater than 72 hours from diagnosis, e.g..: the **FDA/Mayo clinic protocol**[82-83] was the administration of COVID-19 Convalescent Plasma **> 72 hours from diagnosis** during the Cytokine Cascade phase and the Bradykinin Storm phase of the pathophysiology of the coronavirus SARS-CoV-2 across this

nation instead of being given within <72 hours of diagnosis during the Viremia phase of the disease when ***Passive Immunization*** is most effective.[84-92,120] The published articles by Michael Joyner, M.D., *et al.* all demonstrated a survival advance of COVID-19 Convalescent Plasma which were ignored and all the publications concluded that there would be decreased mortality if given within 72 hours of diagnosis.[93-105] At a national public health level, this delay in administration or withholding of COVID-19 Convalescent Plasma was and is tantamount to medical malpractice of our society condoned and advanced previously by your U.S. Department of Health and Human Services akin to the Tuskegee Syphilis Project of the mid-twentieth century.[106-108]

The index incidence of this medical malfeasance was initiated on March 2, 2020[109], before President Trump in the Cabinet Room of *the White House* when Dr. Leonard Schleifler, M.D., CEO of Regeneron, euphemistically stated the term: "**Passive Vaccination**" which merged mistakenly the terms of (1) ***Active Immunization*** (**vaccination** which is prophylaxis requiring at least 14 days after inoculation for the individual to development adequate levels of endogenous IgG) internally with (2) ***Passive Immunization*** (treatment with exogenous IgG). Dr. Schleifler's faulty euphemism, "**Passive Vaccination**", was witnessed by several federal physicians. All the physicians[109] remained silent in the room including the Federal physicians--including Anthony Fauci, M.D., Robert Redfield, M.D., Steven Hahn, M.D., and Anne Schuchat, M.D. from agencies of HHS and 1 U.S. Department of State physician, Deborah Birx, M.D. All the physicians in the Cabinet Room that day should have known the distinct difference between ***Active*** and ***Passive Immunization*** from their introductory Medical School Immunology Courses of the first two basic science years of medical school but did not point this out thus failing the American people! What misadventures progressed over the first months (March and April 2020) of the American COVID-19 epidemic directly followed this fallacious euphemism to the present day.

During the summer of 2020, members of the White House COVID-19 Committee took President Trump to the Charles Drew, M.D., F.A.C.S. Memorial Blood Bank of the American Red Cross (5 blocks away from *The White House* to explain the virtues of **COVID-19 Convalescent Plasma** (a ***Passive Immunological*** agent).[110-111] President Trump left the meeting seemingly elatedly enlightened regarding early treatment with exogenous immunoglobulins (<72 hours from diagnosis) of COVID-19 Convalescent Plasma. He called enthusiastically for immediate implementation. Unfortunately, for maximum-political-optimized-benefit, the initiation of this plan was delayed until August 23, 2020, to be proclaimed on that Sunday evening to the Nation on national television just prior to the start of the Republican National Convention.[112] Dr. Fauci, M.D. in his recent biography, *On Call—A Doctor's Journey in Public Service*[113,114]--blamed this debacle of August 23, 2020, on Dr. Hahn, M.D.'s (former FDA Commissioner) by his presentation and misinterpretation of the initial results <u>of those treated only in <72 hours during the FDA/Mayo Clinic protocol</u>.[115] The FDA document definitively demonstrated increased survival advantage of COVID-19 Convalescent Plasma when given within <72 hours of diagnosis with COVID-19 Convalescent Plasma (a p value $\leq$ 0.03) on August 23, 2020.[116] A month later on September 23, 2020, FDA Commissioner Hahn's testimony before Congress reinforced refined and expanded results confirming that there was a survival advantage of COVID-19 Convalescent Plasma when given within 72 hours of diagnosis across age groups.[117]

Please note that the subliminal false assumption that was made throughout RCT (randomized controlled trials) was that the adult U.S. COVID-19 mortality was regardless of the age of the patient. Using the CDC mortality numbers by decade, adults after age 50 had an increasing mortality rate of 0.5% per year increasing from 50 years of age. Please see the attached graph based (Attachment VIII)[69 (pg4)] on CDC mortality rates reporting by decades of life over the first year of the American COVID-19 epidemic 2020-2021.

Within the first two weeks of October 2020, President Trump, HUD Secretary Ben Carson, M.D., former New York Mayor, Rudy Guiliani, and former New Jersey Governor Christopher Christie tested positive for COVID-19, were all symptomatic, and all were immediately given (within 72 hours of diagnosis) both monoclonal antibodies (***Passive Immunization***) and Remdesivir (antiviral).[118] They all responded and survived as is consistent with the standard response as outlined in the Infectious Diseases Textbook of ***Plotkin's Vaccines***. [A copy/(Attachment VII)--of chapter 8 from the 7th edition is contained within this mailing, although it is also available on the Internet.[119]) Due to Mosby Publishing's dedication to education, Mosby made the entire chapter 8 available to everyone[119] (page 88 of hardcopy[120]):

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

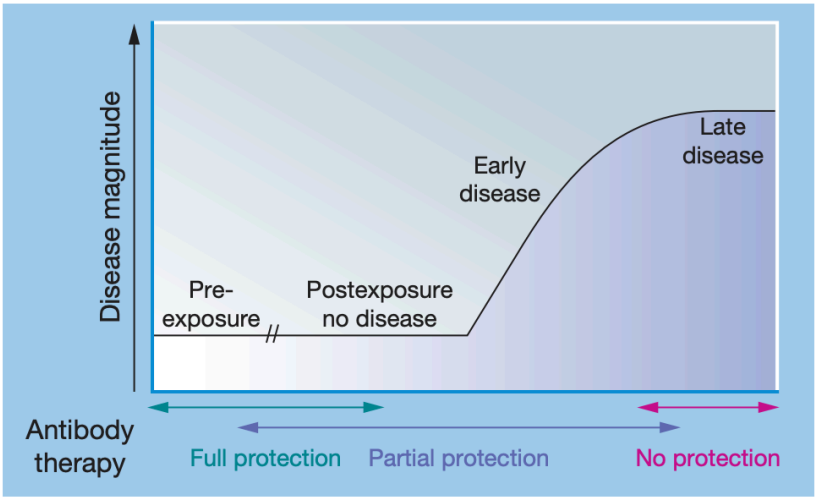


Figure 8.2. Efficacy of passive immunity decreases with disease progression. Full protection from symptomatic disease is best achieved through prophylactic administration of antibody therapy prior to exposure or infection. However, antibody therapy may also be highly effective at early points postexposure, prior to the onset of disease symptoms. Passive immunity is generally less effective when administered after the onset of symptomatic disease, and typically shows little to no clinical benefit once severe late-stage disease has occurred.

With this mailing, I will send you a newly purchased copy of the 7th edition of ***Plotkin's Vaccines***[120] since it is the definitive textbook source on vaccines--even though you, the Secretary of HHS, can obtain a copy of this text from the NIH National Library of Medicine which is under your supervision. While President Trump jubilantly proclaimed that he was "cured", neither[121] **(1)** ***Passive Immunization*** [e.g.: COVID-19 Convalescent Plasma or Sera, Regeneron's REGN-COV2 monoclonal antibody cocktail: casirivimab (REGN10933) and imdevimab (REGN10987), nor Eli Lilly's monoclonal antibody: Bamlanivimab (LY-CoV555)] with **(2)** Remdesivir / VEKLURY [the FDA approved (October 22, 2020) intravenously administered prescription drug] ever became--nor was it ever implemented--as a standardized protocol--WHICH IT SHOULD HAVE BECOME![23,62-64,68-71] When the coronavirus, SARS-CoV-2 mutated to the omicron variant, the monoclonal antibodies and monoclonal antibody cocktails became ineffectual and the unitary focus on prophylaxis with mRNA vaccines had become dominant.[122-126] Only ***Passive Immunization***, COVID-19 Convalescent Plasma, with an antiviral given within 72 hours of diagnosis continues to be the best / most consistently effective immunotherapy treatment of acutely-infected, unvaccinated individuals with coronavirus SARS-CoV-2.

Prior to the development and implementation of mRNA vaccines which are not treatments but prophylaxis by vaccination with endogenous immunoglobulins, a million of untreated, acutely-ill-with-COVID-19 Americans died prior to the mass vaccination. Those individuals could potentially have survived but for the *de facto* withholding of exogenous immunoglobulins (***Passive Immunization***). In essence, they have become footnotes in medical history; and, with the development of vaccines, further development of new monoclonal immunoglobulins was forgotten. Today, regardless of vaccination status, when there is a new diagnosis of infection in all individuals of COVID-19, Paxlovid (an antiviral) is the only available TREATMENT and should be initiated within 5 days for a five-day course.[126] This is the ONLY outpatient treatment available regardless of vaccination status of the acutely infected individual within 72 hours of diagnosis.[127] Unfortunately, Paxlovid has now become financially prohibitive for most Americans as a one five-day course is approximately $1400 per individual per five-day course with Pfizer having more than doubled its retail price from that which it Pfizer charged the U.S. government during the Pandemic.[127] (Secretary Kennedy, maybe you could have the U.S. PHS and the CDC look into this situation.)

Ongoing COVID-19 Convalescent Plasma (***Passive Immunization***) changes with time as the virus mutates but it is an always available updating/renewable *passive immunization* therapy (not prophylaxis). Unfortunately, it was discredited by:

(1) an underpower, statistically skewed[128] RCT (Randomized Controlled Trial) named SIREN-C3PO study[129] that was funded by the NIH NCT04355767;

(2) of which without reporting the statistics of this RCT for peer review was acted upon by the FDA in March 10, 2021, to dismiss the availability of COVID-19 Convalescent Plasma[129]; and

(3) with delayed publication of the results (probably due to the disgraceful statistics throughout the article), on August 18, 2021, and in the republication on November 18,

2021, in *The New England Journal of Medicine*: Korley FK, *et. al.*: Early convalescent plasma for high-risk outpatients with Covid-19[130], ***Passive Immunization*** in the form of COVID-19 Convalescent Plasma was incorrectly dealt a death blow.

Shame on the NIH, the FDA, and *The New England Journal of Medicine.*

Like COVID-19 and the measles, the agencies now under your direction as Secretary of the Department of Health and Human Services (HHS) have failed the American people with regards to Respiratory Syncytial Virus (RSV) for the last quarter of a century as well.[62-64,67-72,131-138] The monoclonal antibody Palivizumab (Synagis) (***Passive Immunization***) was approved by the FDA in 1998. The FDA limited its use to only the prophylaxis by five monthly doses to be rationed / restricted to only high-risk neonates (with congenital heart disease or history of severe respiratory failure in infancy) instead of being given within 72 hours of RSV diagnosis as a treatment to everyone! Over that period of time according to the CDC estimates of an annual incidence of RSV in 60-year-olds and above, about 124,000 (6549 annually mean from 1999-2018) have died from RSV in the United States.[136-138] Instead of treatment, the RSV vaccine prophylaxis (**Active Immunization**—stimulating endogenous antibodies) of Pfizer is now being heavily advertised on television to those over the age of 60 (and now in high risk individuals from ages 18-59)[139] without the establishment of treatment with exogenous antibodies—***Passive Immunization***—in the form of monoclonal antibodies, to all those of any age not vaccinated or immunosuppressed who contract RSV within 72 hours of diagnosis. This should be the ***Passive Immunization*** protocol for treatment of RSV nationally. Also, it has become protocol for all pregnant mothers to be vaccinated against RSV between 32-36 gestational weeks[140] which will protect the mother for the rest-of-her life; but it will protect the baby by ***Passive Immunization*** with the passage of the maternal antibodies via the placenta in decreasing effectiveness over the first 2-3 months of life post-delivery as the circulating half-life of the RSV IgG in the child is approximately 10-21 days.[141] After the first few months of life, there are no maternal immunoglobulins remaining and the child is once again immunologically naïve to RSV.

Mr. Secretary, your initial response to this letter will most likely be incredulous disbelief—BUT, as this letter is coming from a former federal physician and surgeon of 25 years of service within the Veterans Health Administration of the U.S. Department of Veterans Affairs[142]; and, as you are the Secretary of the U.S. Department of Health and Human Services, it is my obligatory duty to remind you that you have a fundamental responsibility to advocate for all of the American people with an educated understanding of that which is known to the individuals within the agencies of the U.S. Department of Health and Human Services who are under your supervision. You have multiple individuals who are experts within the agencies under your direction who can advise you. I would be honored to discuss with you the specifics and nuances of this letter and my previous documentation submitted to **NIH NIAID case file #12276**[143] over the last five years. Two of the "experts" that you should call upon to help interpret this letter for you would be Peter Marks, M.D., PhD, Director of the FDA's Center for Biologics Evaluation and Research (CBER)[97,99,100,103,112,**144**] and John Farley, M.D., MPH, Office Director of the FDA's Center for Drug Evaluation and Research (CDER)[145-148,] whose Centers oversee all biologics including convalescent plasma, monoclonal antibodies and antibody cocktails, biologic plasmas and sera, vaccines, etc. and all drugs including Remdesivir, Paxlovid, etc., respectively. Please see the

present list of Immunoglobulins approved by the FDA as treatments (***Passive Immunization***) against viruses, bacteria, toxins, and envenomations.[20]

Historically, Mr. Secretary, if you address the present issues outlined above--as President Theodore Roosevelt did regarding public health issues of his time over a century ago that resulted in the establishment of the FDA[149,150] —it is possible, you will also leave a significant positive footprint on all the agencies under your auspices as Secretary of the U.S. Department of Health and Human Services (HHS) for the generations to come. With this mailing, I conclude with the attachment of a copy of an article I wrote two decades ago which is in the official published files of the Joseph and Rose Kennedy Bioethics Library of Georgetown University (the Bioethics repository for the NIH NLM, HHS) through the unsolicited request six months after publication of the librarian, Ms. Goldstein, in January 2004: Andrus CH, *et.al. "To Err is Human": Uniformly Reporting Medical Errors and Near Misses, A Naïve, Costly, and Misdirected Goal.*[151] The article concludes with that which is *apropos* for all Medicine *ad infinitum*:

As Francis W. Peabody, MD, told the students of the Harvard Medical School more than 70 years ago:

"…the secret of the care of the patient is caring for the patient."

Secretary Kennedy, you have been confirmed by the U.S. Senate into one-of-the-most honorable, humane, ethically-demanding positions indispensable to the American people, U.S. Government, U.S. Medicine, and U.S. History. You are *de facto* charged as our representative for the healthcare of all those that live in the U.S.A. and its protectorates to fulfill Dr. Peabody's admonition to care for every patient as a unique individual to the best of your abilities--and their care as individuals is collectively paramount for all of us! God's Speed, Mr. Secretary, in your striving towards fulfilling this noble goal.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.[142]
Retired, Professor and Surgeon, Saint Louis University School of Medicine
Retired, Attending Physician and Surgeon of "officially" a quarter of a century, Veterans Health Administration, U.S. Department of Veterans Affairs

ATTACHMENTS:

1. **Attachment I:** Reference #62: Attachment I 2025-02-14 Letter to Marrazzo NIAID 12276
   A hardcopy with this mailing and also digitally in SDHC disc as a file: ***0.2 Attachment I 2025-02-14 Letter to Marrazzo + Inspectors General NIAID 12276***

2. **Attachment II:** Reference #63: Attachment II Submissions to the *Internet Archive* over last five years, **NIH NIAID case file: 12276**: Books 1, 2, 3, 4
   0.3 Attachment II Submissions to the Internet Archive copy2.dox also can be located in the index of the January 18, 2025 letter to President Joseph Biden (Attachment III that follows[68]) A hardcopy with this mailing and also digitally in SDHC disc as a file: ***0.3 Attachment II Submissions to the Internet Archive copy 2***

3. **Attachment III:** Reference #68: Cover letter to President Joseph Biden of January 18, 2025, ***0.4 Attachment III Ltr to President Biden Scan2025-01-18_112330.jpg*** as the face sheet for the spiral-bound binder included in this mailing. All of that which is in the spiral-bound binder is digitally contained in SDHC as folder: ***Sent to NIAID 12276 Feb 14, 2025 copy***

4. **Attachment IV:** Reference #69: Andrus CH: Generalized Dismissal of Early Treatment with *Passive Immunization* and Antivirals (Not Prophylaxis/*Active Immunization*) in Persons Infected with COVID-19
   A hardcopy with this mailing and also digitally in SDHC disc as a file: ***0.5 Attachment IV 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals copy***

5. **Attachment V:** Reference #70: **America's Fight Against Coronavirus, SARS-CoV-2, COVID-19** with mRNA vaccine prophylaxis (monoclonal *Active Immunization*) alone *without implementation* FOR ALL infected with COVID-19 with **synergistic, early treatment (<96 hours from diagnosis) with exogenous immunoglobulins (*Passive Immunization*) and antivirals**
   OR
   Euphemistical Obfuscation in Clinical Medicine, *Jesuitical* Lies by Omission and Paltering, Subliminal Bait-and Switch, and Machiavellianism Resulting in 1,000,000+ Deaths and America's Defeat by the Non-sentient Coronavirus, SARS-CoV-2, COVID-19
   A hardcopy with this mailing and also digitally in SDHC disc as a file: ***0.6 Attachment V Euphemistical Obfuscation in Clinical Medicine copy***

6. **Attachment VI:** Reference #71: ***Reductio ad Absurdum:* The COVID-19 Tale of Two Presidents, the Ramifications of Fifty Years of American Scandal, Therapeutic Nihilism, and Medical Stupidity**
   A hardcopy with this mailing and also digitally in SDHC disc as files: ***0.7 Attachment VI Complete 2023-04-28 Tale of Two Presidents***
   0.7 Attachment VI Reductio ad Absurdum—face sheet and references only

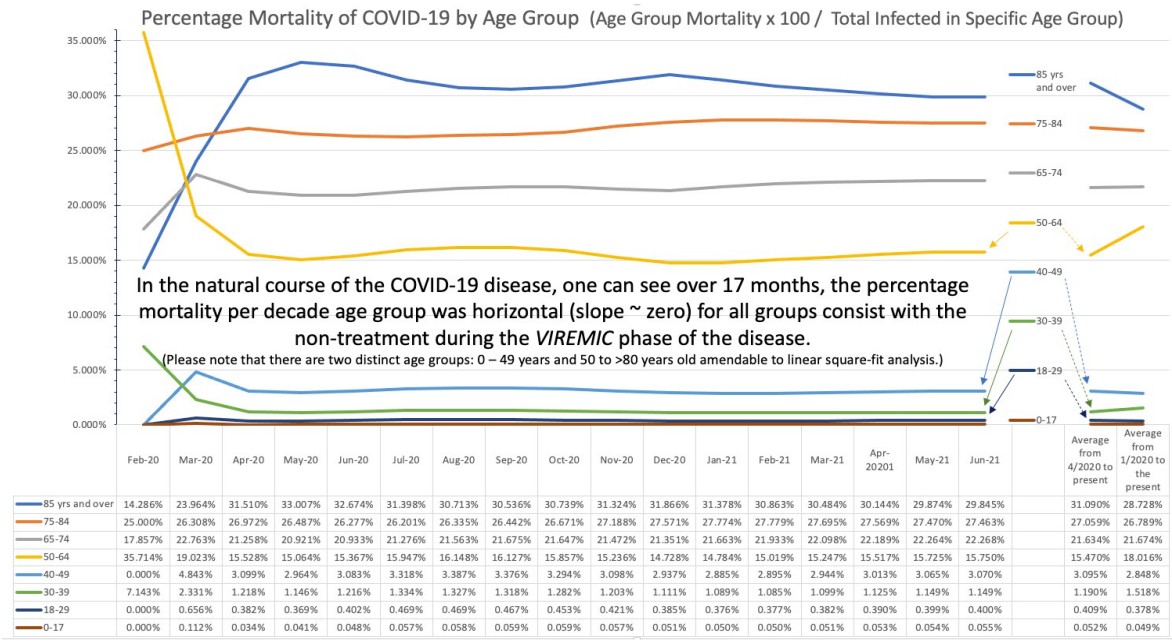
7. **Attachment VII:** Reference #120: Plotkin SA, Orenstein WA, Offit PA, Edwards KM: *Plotkin's Vaccines*, 7th edition. Philadelphia: Elsevier, 2018.—In this mailing.

8. **Attachment VIII:** Reference #69, **pg 24:** Graph IV, fig 1 and fig 2: Plots of the Monthly Percentage Mortality from February 2020 to June 2021 reports of the CDC database of sex and age mortality of COVID-19 which are on the

next page. Graphs the COVID-19 mortality rate by age derived from the CDC data publication from years 2020 and part of 2021. https://web.archive.org/web/2021021715653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge

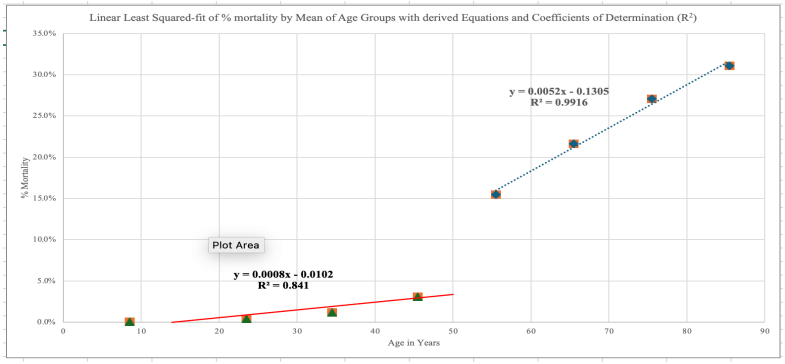
Attachment VIII: 0.1 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals.docx 3/20/25 12:12:00 PM

Graph IV, fig 1 and fig 2: Plots of Monthly Percentage Mortality from February 2020 to June 2021 reports of the CDC database of sex and mortality of COVID-19.[187]


Percentage Mortality of COVID-19 by Age Group (Age Group Mortality x 100 / Total Infected in Specific Age Group)
35.000%
30.000%
25.000%
20.000%
15.000%
10.000%
5.000%
0.000%
85 yrs and over
75-84
65-74
50-64
40-49
30-39
18-29
0-17
In the natural course of the COVID-19 disease, one can see over 17 months, the percentage mortality per decade age group was horizontal (slope ~ zero) for all groups consist with the non-treatment during the VIREMIC phase of the disease.
(Please note that there are two distinct age groups: 0 – 49 years and 50 to >80 years old amendable to linear square-fit analysis.)

	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-20201	May-21	Jun-21		Average from 4/2020 to present	Average from 1/2020 to the present
85 yrs and over	14.286%	23.964%	31.510%	33.007%	32.674%	31.398%	30.713%	30.536%	30.739%	31.324%	31.866%	31.378%	30.863%	30.484%	30.144%	29.874%	29.845%		31.090%	28.728%
75-84	25.000%	26.308%	26.972%	26.487%	26.277%	26.201%	26.335%	26.442%	26.671%	27.188%	27.571%	27.774%	27.779%	27.695%	27.569%	27.470%	27.463%		27.059%	26.789%
65-74	17.857%	22.763%	21.258%	20.921%	20.933%	21.276%	21.563%	21.675%	21.647%	21.472%	21.351%	21.663%	21.933%	22.098%	22.189%	22.264%	22.268%		21.634%	21.674%
50-64	35.714%	19.023%	15.528%	15.064%	15.367%	15.947%	16.148%	16.127%	15.857%	15.236%	14.728%	14.784%	15.019%	15.247%	15.517%	15.725%	15.750%		15.470%	18.016%
40-49	0.000%	4.843%	3.099%	2.964%	3.083%	3.318%	3.387%	3.376%	3.294%	3.098%	2.937%	2.885%	2.895%	2.944%	3.013%	3.065%	3.070%		3.095%	2.848%
30-39	7.143%	2.331%	1.218%	1.146%	1.216%	1.334%	1.327%	1.318%	1.282%	1.203%	1.111%	1.089%	1.085%	1.099%	1.125%	1.149%	1.149%		1.190%	1.518%
18-29	0.000%	0.656%	0.382%	0.369%	0.402%	0.469%	0.469%	0.467%	0.453%	0.421%	0.385%	0.376%	0.377%	0.382%	0.390%	0.399%	0.400%		0.409%	0.378%
0-17	0.000%	0.112%	0.034%	0.041%	0.048%	0.057%	0.058%	0.059%	0.059%	0.057%	0.051%	0.050%	0.050%	0.051%	0.053%	0.054%	0.055%		0.052%	0.049%

Fig 1: Y axis = monthly decade age group mortality due to COVID-19 total population of decade age group, Y axis = mortality rate in %. Data derived from the CDC database of sex and age mortality. https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge [187]


Linear Least Squared-fit of % mortality by Mean of Age Groups with derived Equations and Coefficients of Determination (R²)
% Mortality
Age in Years
y = 0.0052x - 0.1305
R² = 0.9916
y = 0.0008x - 0.0102
R² = 0.841
Plot Area

0 – 49 years of age: Mortality rate (y) = 0.0008 (x) – 0.0102 $r^2 = 0.84$
50 – 90+ years of age: Mortality rate (y) = 0.0052 (x) – 0.1305 $r^2 = 0.99$

Fig 2 is derived from a calculated least-square fit of the data from Fig. 1. The slopes of the plots x 100 equals the fractional increase in mortality rate per year for the 0 – 49 age group of roughly 0.08% increase per age-year of the annual mortality and for the ≥50 age mortality of 0.52% increase per age-year of the annual mortality of ages are: 50 years of age, the calculated risk of mortality rate is: [(0.0052 x 50)-0.1305= 14%; 60 years of age, the calculated risk of mortality rate is: [(0.0052 x 60)-0.1305] = 18.2%; and 70 years of age, the calculated risk of mortality rate is [(0.0052 x 70)-0.1305]= 23.4%.

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Measles (Rubeola) [Pages 3,4 of 16]
GamaSTAN® is indicated to prevent or modify measles in asusceptible person exposed fewer than 6 days previously (2). A susceptible person is one who has not been vaccinated and has not had measles previously. GamaSTAN® may be especially indicated for susceptible household contacts of measles patients, particularly contacts under 1 year of age, for whom the risk of complications is highest (2). GamaSTAN® and measles vaccine should not be given at the same time (2). If a child is older than 12 months and has received GamaSTAN®, he should be given measles vaccine about 5 months later when the measles antibody titer will have disappeared, provided there are no contraindications to the vaccine (1).

If a susceptible child exposed to measles is immunocompromised, GamaSTAN® should be given immediately (3). GamaSTAN® may also be considered for severely immunocompromised individuals exposed to measles regardless of immunization status. Children who are immunocompromised should not receive measles vaccine or any other live viral vaccine (4).

Measles (Rubeola) [Page 9 of 16]
GamaSTAN® should be given in a dose of 0.25 mL/kg to prevent or modify measles in a susceptible person exposed fewer than 6 days previously (1,2). A susceptible child who is exposed to measles and who is immunocompromised should receive a dose of 0.5 mL/kg (maximum dose, 15 mL) of GamaSTAN® immediately (3). The dosage of Immuneglobulin (Human) for exposed individuals who have underlying malignant disease should be 0.5 mL/kg or 15 mL maximum (1).

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Measles (Rubeola) [Page 4 of 16]
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Measles (Rubeola) [Page 9 of 16]
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> **Results**
> A total of 3409 contacts were identified, of which 208 (6.1%), 274 (8.0%), and 318 (9.3%) met the inclusion criteria for analysis of MMR, IG, and any PEP effectiveness, respectively. Of the contacts included, 44 received MMR PEP and 77 received IG PEP. Effectiveness of MMR PEP was 83.4% (95% confidence interval [CI], 34.4%, 95.8%). No contact who received IG PEP developed measles; effectiveness of IG PEP was 100% (approximated 95% CI, 56.2%, 99.8%). Effectiveness of receiving any PEP (MMR or IG) was 92.9% (95% CI, 56.2%, 99.8%).

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Measles
Recommendations

1. For asymptomatic healthcare personnel ***with*** presumptive evidence of immunity to measles (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm#Tab3)[1] who have an exposure to measles:
   • Postexposure prophylaxis is not necessary.
   • Work restrictions are not necessary.
   • Implement daily monitoring for signs and symptoms of measles from the 5th day after their first exposure through the 21st day after their last exposure.
2. For asymptomatic healthcare personnel ***without*** presumptive evidence of immunity to measles who have an exposure to measles:
   • Administer postexposure prophylaxis in accordance with CDC and ACIP recommendations (https://www.cdc.gov/acip-recs/hcp/vaccine-specific/mmr.html)[2]
   • Exclude from work from the 5th day after their first exposure through the 21st day after their last exposure, regardless of receipt of postexposure prophylaxis.
   • Work restrictions are not necessary for healthcare personnel who received the first dose of MMR vaccine prior to exposure:
      -- They should receive their second dose of MMR vaccine as soon as possible (at least 28 days after their first dose).
      -- Implement daily monitoring for signs and symptoms of measles from the 5th day after their first exposure through the 21st day after their last exposure.
3. For healthcare personnel with known or suspected measles, exclude from work for 4 days after the rash appears.

4. For immunocompromised healthcare personnel with known or suspected measles, exclude from work for the duration of their illness.
5. During a measles outbreak, administer measles vaccine to healthcare personnel in accordance with CDC and ACIP recommendations (https://www.cdc.gov/acip-recs/hcp/vaccine-specific/mmr.html).[2]

Narrative

Background …

Occupational Exposures …

Clinical Features …

Testing and Diagnosis …

Postexposure Prophylaxis
Exposed HCP without presumptive evidence of immunity should receive postexposure vaccination as soon as possible in accordance with CDC and ACIP recommendations. In some circumstances, immune globulin may be appropriate to offer these HCP, but this should be done in accordance with CDC and ACIP recommendations (https://www.cdc.gov/acip-recs/hcp/vaccine-specific/mmr.html).[2]

References …

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57. Blog D, Medical Director Division of Vaccine Excellence, New York Department of Health: Measles review for health care providers. Immunize@health.ny.gov 2024 May 22; Slides: 1-55. (See post-exposure prophylaxis, slides 39-41. https://www.health.ny.gov/prevention/immunization/providers/measles/docs/measles_review_for_providers.pdf

58. CDC: Measles (Rubeola), Measles vaccine recommendations.

Post-exposure prophylaxis for measles

People exposed to measles who cannot readily show that they have adequate presumptive evidence of immunity against measles should be offered post-exposure prophylaxis (PEP). Public health officials can help identify eligible persons, assess any contraindications, and weigh benefits.

There are two types of PEP for measles. To potentially provide protection or modify the clinical course of disease among susceptible persons, administer one of these:

- MMR vaccine, if administered within 72 hours of initial measles exposure.
- Immunoglobulin (IG), if administered within 6 days of exposure. The recommended dose for intramuscular immunoglobulin (IMIG) is 0.5mL/kg, regardless of the contact's immune status.

Don't administer MMR vaccine and **IG simultaneously.** This practice invalidates the vaccine.
https://www.cdc.gov/measles/hcp/vaccine-considerations/index.html

59. Montroy J, Yan C, Forbes N, Krishnan, Tunis M, Salvadori MI: Post-exposure prophylaxis for the prevention of measles: A systematic review. Vaccine 2025 February 15; 47, 126706. https://www.sciencedirect.com/science/article/pii/S0264410X25000039?via%3Dihub

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62. Andrus CH: **Attachment I**: Letter to Marrazzo NIAID 12276. A hardcopy with this mailing and also digitally in SDHC disc as a file:
0.2 Attachment I 2025-02-14 Letter to Marrazzo + Inspectors General NIAID 12276

63. Andrus CH: **Attachment II**: 0.3 Attachment II Submissions to the Internet Archive copy.
List of Accompanying Documents to Dr. Andrus' response letter of March 4, 2024, to President Joseph Biden in Dr. Andrus' response to President Biden's letter of July 7, 2023. Submissions to the *Internet Archive* over last five years, **NIH NIAID case file: 12276**: Books 1, 2, 3, 4
0.3 Attachment II Submissions to the Internet Archive copy2.docx also can be located in the index of the January 18, 2025 letter to President Joseph Biden (Attachment III that follows[68]) A hardcopy with this mailing and also digitally in SDHC disc as a file: ***0.3 Attachment II Submissions to the Internet Archive copy 2***

64. Andrus CH: **Book 1:** Andrus CH: *Book 1: Dear Mr. President: COVID-19 and Where We Went Wrong 2023 02 02*. Internet Archive, uploaded: 2023-09-12, pages: 1 - 1266.

NIH NIAID Case #12276. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02/

65. Andrus CH: **Book 2:** Andrus CH: *0 2023 09 11 Scan VA RSSO Case 286816 Letter Arrived Feb 13 2023*. Internet Archive, uploaded: 2023-09-11. NIH NIAID Case #12276. Pages 1-3 plus 5 additional attached .pdf files: https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/0%202023-09-11%20scan%20VA%20RSSO%20Case%20286816%20letter%20arrived%20Feb%2013%202023/

66. Andrus CH: **Book 3:** Andrus CH: *Abridged Dear Mr. President: "…to care for him who shall have borne the battle…"A. Lincoln* Internet Archive, uploaded: 2024-02-29, pages 1-534. NIH NIAID case #12276 https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-the-battle-2024-02-29

67. Andrus CH: **Book 4:** Andrus CH: *Book 4: Biden Response to The Summary of Book 1 COVID 19 And Where We Went Wrong*. Internet Archive, Uploaded 2024 Feb 05, **[Only 382 pages loaded]** https://archive.org/details/book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong/ , ***** Uploaded again on March 5, 2024 to the Internet Archive and all 848 pages were uploaded. Title: 0.4 Book 4 Biden response to the Summary of Book 1 COVID 19 And Where We Went Wrong 2nd Attemp , *Internet Archive* , uploaded March 5, 2024.** pages 1- 848 https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp *** NIH NIAID Case #12276.

68. Andrus CH: **Attachment III:** Cover letter to President Joseph Biden of January 18, 2025, ***0.4 Attachment III Ltr to President Biden Scan2025-01-18_112330.jpg*** as the face sheet for the spiral-bound binder included in this mailing. All of that which is in the spiral-bound binder is digitally contained in SDHC as folder: ***Sent to NIAID 12276 Feb 14, 2025 copy:***

Name	Date Modified	Size	Kind
0.1 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals	Today at 9:41 AM	10.3 MB	Microso...(.docx)
0.2 Attachment I Euphemistical Obfuscation in Clinical Medicine	Dec 13, 2024 at 5:52 AM	301 KB	Microso...(.docx)
0.3 Attachment II Submissions to the Internet Archive	Dec 13, 2024 at 5:55 AM	273 KB	Microso...(.docx)
0.4 Attachment III Reductio ad Absurdum	Dec 13, 2024 at 5:57 AM	4.8 MB	Microso...(.docx)
0.5 Attachment IV Validation letter from the NIH NIAID establishing NIAID Case # 12276	Dec 13, 2024 at 6:17 AM	8.7 MB	Microso...(.docx)
0.6 Attachment V 1977 NEJM letter of Case of Chronic Denial with Alfred Gilman response	Dec 13, 2024 at 6:03 AM	921 KB	Microso...(.docx)
0.7 Attachment VI Tables re Sources Definitions and Statistics	Dec 13, 2024 at 6:06 AM	627 KB	Microso...(.docx)
0.8 Attachment VII Letters to Members of Congress and Pres Trump 8_23_2020 and 8_28_2020	Dec 12, 2024 at 10:20 AM	3.4 MB	Microso...(.docx)
0.9 Attachment VIII 08 076.0 2021-09-19 Tragedy of Electronic Overwriting	Dec 31, 2024 at 11:29 AM	635 KB	Microso...(.docx)
1.0 REFERENCES of ATTACHMENTS I - VIII	Dec 13, 2024 at 11:48 AM	264 KB	Microso...(.docx)
2.1 Table 1- Digital vs. Analog—Yes, No, Maybe in Medicine and Treatment of Covid-19	Dec 13, 2024 at 6:33 AM	2.1 MB	Microso...(.docx)
2.2 Definitions_Fundamentals_Legal_Mandates background	Dec 13, 2024 at 6:13 AM	33 KB	Microso...(.docx)
2.3 2024-11-23 Tables 2-6	Dec 12, 2024 at 10:44 AM	5.9 MB	Microso...(.docx)
2.4 References for Tables 1 – 6	Dec 13, 2024 at 6:39 PM	2.1 MB	Microso...(.docx)
3 2024-11-23 Some Pertinent Transcripts and Excerpts	Nov 23, 2024 at 6:25 AM	2.9 MB	Microso...(.docx)

69. Andrus CH: **Attachment IV:** (from reference 68 in spiral bound book in submission above): Andrus CH: Generalized Dismissal of Early Treatment with *Passive Immunization* and Antivirals (Not Prophylaxis/*Active Immunization*) in Persons Infected with COVID-19. A hardcopy with this mailing and also digitally in SDHC disc as a file: ***0.5 Attachment IV 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals copy***

70. Andrus CH: **Attachment V:** (from reference 68 in spiral bound book in submission above):
Andrus CH: **America's Fight Against Coronavirus, SARS-CoV-2, COVID-19** with mRNA vaccine prophylaxis (monoclonal *Active Immunization*) alone *without implementation* FOR ALL infected with COVID-19 with **synergistic, early treatment (<96 hours from diagnosis) with exogenous immunoglobulins (*Passive Immunization*) and antivirals**

OR

Euphemistical Obfuscation in Clinical Medicine, *Jesuitical* Lies by Omission and Paltering, Subliminal Bait-and Switch, and Machiavellianism Resulting in 1,000,000+ Deaths and America's Defeat by the Non-sentient Coronavirus, SARS-CoV-2, COVID-19

A hardcopy with this mailing and also digitally in SDHC disc as a file:
0.6 Attachment V Euphemistical Obfuscation in Clinical Medicine copy

71. Andrus CH: **Attachment VI:** (from reference 68 in spiral bound book in submission above): Andrus CH:
***Reductio ad Absurdum*: The COVID-19 Tale of Two Presidents, the Ramifications of Fifty Years of American Scandal, Therapeutic Nihilism, and Medical Stupidity:**

Euphemisms[239]**:** Experimental / Investigational / EUA,
Expanded Access / Compassionate Care
FDA Authorization vs FDA Approval,
Treatment vs Prophylaxis,
Active Immunization vs Passive Immunization, etc.,

FDA Archiving reliance on non-governmental sites
FDA archived web material is maintained within the Pagefreezer platform.

and loss of information by ***electronic overwriting*** and ***destruction*** of URLs,

FDA and NIH blatant, total disregard of the Right to Try Act (PL-115-176) by never declaring a completed Phase 1(Safety) [vs Phase 2/3 Efficacy]
Clinical Trial and thus dismissing and *de facto* legally violating PL-115-176

Statistical Misdirection,

Predatory Marketing, and

> 1.1 million Americans dead associated with **withholding early** (**within 72-120 hours** of diagnosis) synergistic treatment with **Exogenous Immunoglobulins (Passive Immunization)** and **Antivirals**

Contingent on: Ignorance, Sins of Ommission, Conflicts-of-Interest, Greed

"Reform must come from within, not from without.
You cannot legislate for Virtue" James Cardinal Gibbons, "Prince of Democracy"

Face page of ***Reductio ad Absurdum*** with references only, pages 1-29. Complete section can be found in pages e30 – e130 of *0.4 BOOK 4 Biden Response to the Summary of Book 1 COVID 19 And Where We Went Wrong 2nd Attemp*, publication date 2024-03-05.

https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp and also:

A hardcopy with this mailing and also digitally in SDHC disc as files:
0.7 Attachment VI Complete 2023-04-28 Tale of Two Presidents
0.7 Reductio ad Absurdum—face sheet and references only

72. GPO: FDLP—Federal Depository Library Program. 44 U.S.C. § 19. https://www.gpo.gov/how-to-work-with-us/agency/services-for-agencies/federal-depository-library-program#:~:text=The%20Federal%20Depository%20Library%20Program%20%2844%20U.S.C.%20%C2%A7,depository%20libraries%20throughout%20the%20U.S.%20and%20its%20territories.

73. Kahle B: Internet Archive – An American non-profit digital library website founded in 1996. https://archive.org/

74. Pogue D: The Wayback Machine, a time machine for the web.--The *Internet Archive*, CBS NEWS Sunday Morning, aired 23 June 2024. https://www.cbsnews.com/news/the-wayback-machine-a-time-machine-for-the-web/

75. Internet Archive: Wayback Machine. https://web.archive.org/

76. 107th Congress: Sarbanes-Oxley Act of 2002. Public Law 107-204, 116 STAT. 745, July 30. 2002. https://www.congress.gov/107/statute/STATUTE-116/STATUTE-116-Pg745.pdf

77. Supreme Court of the United States: Syllabus, FISCHER *v.* UNITED STATES, CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT, No. 23-5572. Argued April 16, 2024—Decided June 28, 2024. https://www.supremecourt.gov/opinions/23pdf/23-5572_l6hn.pdf

78. Congressional Research Service: *Fischer v. United States*: Supreme Court reads federal obstruction provision narrowly in capitol breach prosecution. CRS Legal Sidebar, Prepared for Members and Committees of Congress, updated July 10, 2024. https://crsreports.congress.gov/product/pdf/LSB/LSB11126

79. Gulick RM, Pau AK, Daar E, Evans L, Gandhi RT, Tebas P, Ridzon R, Masur H, Lane HC, and the NIH COVID-19 Treatment Guidelines Panel. Ann Internal Medicine 2024;177: 1547-1557. https://www.acpjournals.org/doi/full/10.7326/ANNALS-24-00464?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org , https://www.acpjournals.org/doi/10.7326/ANNALS-24-00464

80. NIH: NIH Treatment Guidelines. From April 2020, the NIH COVID-19 Treatment Panel published over the subsequent the four-year interval to the last publication of the *NIH COVID-19 Treatment Guidelines* of February 29, 2024 (and subsequent discontinuation

of the URL by the NIH on https://www.covid19treatmentguidelines.nih.gov of August 16, 2024)[79]:

On August 16, 2024, the NIH officially removed direct electronic access to the NIH COVID-19 Treatment Guidelines by removing the URL: https://www.covid19treatmentguidelines.nih.gov/ from the Internet. Using the Wayback Machine, one could find that the guidelines were captured by the *Internet Archive* 4,983 times between April 21, 2020 and August 17, 2024: https://web.archive.org/web/20250000000000*/https://www.covid19treatmentguidelines.nih.gov/

- As was stated in the *Annals of Internal Medicine* of November 2024[79]:

> Development of treatment guidelines is not a typical role for the U.S. Department of Health and Human Service (HHS) and the National Institutes of Health (NIH); rather, such guidelines are usually developed by professional societies or the Centers for Disease and Prevention (CDC). However, given the NIH's long experience in creating HIV treatment guidelines, HHS requested that the NIH take the lead in expeditiously creating **"living"** treatment guidelines for COVID-19 that would be both widely accessible and frequently updated as important new information became available. This mandate posed special challenges in terms of obtaining sufficient time and attention from experts who were also responsible for their local institutional COVID-19-related clinical activities. Additional challenges included obtaining administrative support for coordinating operations, editing, and website management.
>
> The NIH COVID-19 Treatment Guidelines (the Guidelines) were intended not as a mandate for clinicians or patients but as one source of credible expert advice that would evolve over time as additional data became available to inform therapeutic management strategies. The first release of the Guidelines was on 21 April 2020.
>
> With the declaration of the end of the COVID-19 public health emergency (1,2), the NIH has determined it is now appropriate to sunset the NIH COVID-19 Treatment Guidelines. Drugs approved by the U.S. Food and Drug Administration (FDA) for treatment of COVID-19 are now available; outcomes for patients with COVID-19 are currently much better than in 2020 to 2022; and other organizations, such as the American College of Physicians, the Infectious Disease Society of America, the Pediatric Infectious Diseases Society, the World Health Organization, now provide readily accessible guidelines of their own (3-6).
>
> The last update to the Guidelines (Supplement 1, available at Annals.org) was posted on 29 February 2024. All of the archived versions of the Guidelines from April 2020 to the last release are available at https://wayback.archive-it.org/4887/20240626155844/https://www.covid19treatmentguidelines.nih.gov ***[https://www.covid19treatmentguidelines.nih.gov can thus only be found today through the Wayback Machine of the Internet Archive.]***

For all of history, the U.S. National Institutes of Health (NIH) has figuratively, circuitously, electronically **discontinued the path to** their contributions to the guidelines they advanced during the American COVID-19 epidemic which, at the time, they claimed were "… 'living' treatment guidelines for COVID-19." **Shame on the NIH** and shame on us all! I would allege, the NIH represents, in this case all of U.S. Medicine which essentially destroyed (or at least obfuscated) for all of history: the knowledge, the logic, the therapeutic intent, etc.--truths and errors--that were functionally driving our addressing of the American epidemic caused by the coronavirus, SARS-Cov-2, COVID-19, that confronted the people of the United States of America from 2020 to the present day--and, is still endemically, ongoing!

> The Guidelines consisted of 90 pages in the first iteration, 278 pages at the end of 12 months, and 478 pages in the last edition. Forty pages were archived when their contents were deemed to no longer be relevant for clinicians. From 21 April 2020 until the final update on 29 February 2024, the Panel voted on recommendations 438 times (Table 5 of **Supplement 2**).
>
> In total, there were 71 updates of the Guidelines from April 2020 through February 2024. As shown in **Figure 1**, updates, rapid communications, and revisions were initially frequent and then slowed in 2023 and 2024. These were generally driven by the release of data from clinical trials, information from other publications that was important to therapeutic management, or announcements from the FDA.
>
> From the beginning of the pandemic through February 2024, the FDA issued 17 emergency use authorizations (EUAs) for COVID-19-related drugs. Of these 17 17 EUAs, 4 of the drugs (hydroxycholoroquine, COVID-19 convalescent plasma, anakinra, and vilobelimab) were not recommended for use by the Panel. **Figure 2** shows the timing of FDA actions for preventive and therapeutic products related to management of COVID-19 from March 2020 to February 2024.
>
> As of 29 February 2024, the Guidelines had received more than 50 million page views from more than 26 million users. The number of unique users (**Figure 3**) and page views closely followed the curve of pandemic hospitalizations in the United States. Unpredictable surges in caseloads highlighted the importance of keeping the recommendations current. Although most page views were from the United States, approximately 20% to 25% were from other countries, notably Australia, Canada, India, Japan, Malaysia, Mexico, and Thailand.

The sunsetting by electronic overwriting and paltering iterations of *NIH COVID-19 Treatment Guideline* has been tantamount to the destruction of the 72 URLs of the *NIH COVID-19 Treatment Guidelines* akin to a Nazi book burning[81] but stealthily in American society today. Such electronic sunsetting may be dutifully an electronic preservation of all 72 iterations on the computerized server farm of the *Internet Archive*--a non-governmental, non-profit 501(c)(3) institution[73-75]; but in reality, though, the electronic sunsetting of medical history is subtly obfuscative; intricately, minimally discoverable; and surreptitiously destructive of human knowledge. I would allege that as the NIH is an agency of the U.S. Department of Health and Human Services (DHHS), the electronic sunsetting of the *NIH COVID-19 Treatment Guidelines* is a violation of the intent of the Sarbanes-Oxley Act of 2002, 18 U.S.C. §15129(c)(1).[76-78] Such electronic-storage-only is unintellectually and unethically suppressive by the *de facto* failure to the preserve tangibly in an accessible hardcopy format for future generations the trials and tribulations and accomplishments and mistakes in our society's most-recent attempts at the advancement of human knowledge regarding COVID-19. Instead of disguising the 72 iterations of the NIH COVID-19 Treatment Guidelines[80] from future medical practitioners, every hospital and medical school library in the U.S.A. should printout all 72 iterations and shelve them as a medical series physically in their tangible Reference sections, e.g.: Using a computer and a color laser printer, one can printout each iteration from the *Internet Archive*[73-75] for inclusion in such a medical reference series with just a half-a-ream of paper, 4 printer cartridges, binding materials, and approximately 15 minutes of computer printer time and human effort (72 iterations x ¼ hour = 18 man-hours /library).—that, to me, seems like a bargain in the preservation of the present medical thought process for all of history.

81. Stern G: The burning of the books of Nazi Germany: The American Response. Museum of Tolerance, Los Angeles. https://www.museumoftolerance.com/education/archives-

and-reference-library/online-resources/simon-wiesenthal-center-annual-volume-2/annual-2-chapter-5.html

82. 2020-04-03 Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19. (CDC recommendation started January 31, 2020 to present with last overwriting update Feb 16, 2021. http://web.archive.org/web/20200408110417/https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html by the *Internet Archive,* between January 31, 2020, and March 13, 2025, there were ongoing iterations of 3,934 times: https://web.archive.org/web/20250000000000*/https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

    FDA/Mayo Clinic: Expanded access to convalescent plasma for the treatment of Patients with COVID-19 https://www.uscovidplasma.org/ by the *Internet Archive,* between April 4, 2020, and March 16, 2025, there were ongoing iterations with 1,596 saved times: https://web.archive.org/web/20250000000000*/https://www.uscovidplasma.org/

83. 2020-04-04 Joyner M, (Principal Investigator): COVID-19 expanded access program -- Convalescent Plasma COVID-19 (coronavirus) Treatment – Mayo Clinic. First date digitally preserved by the Internet Archive (Wayback Machine). –Origin of the FDA/Mayo Clinic expanded access program. **(Compassionate Use—can't be used for Randomized Controlled Trials by definition of the NIH and FDA)** https://web.archive.org/web/20200404010134/https://www.uscovidplasma.org/ by the *Internet Archive,* between April 4, 2020, and March 4, 2055, there were ongoing iterations saved 1,594 times: https://web.archive.org/web/20250000000000*/https://www.uscovidplasma.org/

> The protocol requires the patient or family member to consent to receiving plasma from someone who has recovered from COVID-19. Their plasma has substances that could improve chances of recovery. Only hospitalized patients referred by their health care provider will participate in this protocol.
>
> Hospitalized patients are eligible to receive convalescent plasma if:
>
> - They are 18+ years of age
> - They have laboratory-confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19
> - They are admitted to an acute care facility for the treatment of COVID-19 complications
> - They have severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
> - There is informed consent provided by the patient or healthcare proxy
>
> Severe COVID-19 is defined by one or more of the following:

- Shortness of breath (dyspnea)
- Respiratory frequency ≥ 30/min
- Blood oxygen saturation ≤ 93%
- Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- Lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:

- Respiratory failure
- Septic shock
- Multiple organ dysfunction or failure

Michael J. Joyner, M.D., Summary, Mayo Clinic.
https://www.mayo.edu/research/faculty/joyner-michael-j-m-d/bio-00078027

84. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JWM, Brüggermann RJ, van der Hoeven H: Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. Pre Prints: Posted Not PEER-reviewed. 2020 April 3 https://www.preprints.org/manuscript/202004.0023/v1

85. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Chen Z, Zhang X, Yang X: Reply to Kesici et al. and Zeng et al.: Blocking the virus and reducing the inflammatory damage in COVID-19. Proceedings of the National Academy of Sciences. 2020-June 20 https://www.pnas.org/content/117/23/12529

> First of all, this study was a pilot trial and the aim was to investigate the safety of CP transfusion, which was defined as the primary endpoint (3). We nevertheless also explored the possible therapeutic benefits of CP by examining its effectiveness in neutralizing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in ameliorating clinical symptoms and paraclinical criteria in recipients. Indeed, the adverse effect was minor, whereas a quickly improved outcome of 10 severe COVID-19 patients was observed. There are of course a number of issues to be addressed, such as the confirmation of the clinical effectiveness in a phase II controlled, randomized trial.
>
> Second, the objective for CP transfusion in severe COVID-19 therapy is based on an in-depth understanding of disease mechanisms. The pathogenesis of this epidemic involves the interaction between viral replication of SARS-CoV-2 and human immune response (4). Particularly, in severe or critical COVID-19 cases, lung alveolar macrophages or epithelial cells could produce various proinflammatory cytokines and chemokines, which recruit monocytes and neutrophils to the infection site to clear the virus particles and infected cells, resulting in uncontrolled inflammation. The uncontrolled virus infection leads to more macrophage infiltration and a further worsening of lung injury. Therefore, the key point of CP therapy is to neutralize the virus and to interrupt the vicious cycle of excessive activation of the immune response in severe patients. In our study, 200 mL CP containing neutralized antibody above 1:640 rapidly cleared the viremia and achieved clinical improvement. Considering the accessibility of plasma donors, using CP as replacement fluid for the therapeutic plasma exchange may be not feasible.
>
> Third, the optimal treatment time and dose of CP need to be determined by the knowledge on viral proliferative kinetics. Zhou et al. (5) reported that the median viral shedding time was 20.0 d in

survival patients. Huang et al. (6) observed that the viral load gradually decreased in the respiratory tract after 7 d of illness onset but can be detected after 28 d of illness onset in two-thirds of critically ill patients. Chen et al. (7) found the serum viremia was detected in 29.4% (5/17) critically ill patients and was significantly correlated with the level of interleukin-6. Thus, monitoring the dynamic changes of interleukin-6 level, which was significantly elevated in COVID-19, may help to determine the optimal treatment time, generally within 2 wk.

Finally, the optimal time for collecting CP should be determined by the time and level of total antibody production in convalescent patients. The presence of antibodies was <40% among patients within 1 wk since onset and rapidly increased to 100.0% (antibody), 94.3% (immunoglobulin M), and 79.8% (immunoglobulin G [IgG]) since day 15 after onset (8). Also, the neutralizing antibody titer was correlated with the IgG antibodies (9). The median duration of hospitalization for COVID-19 patients was 12.0 d (**10**). In our study, all of the donors were recovered from the common type of COVID-19. Therefore, the collection of CP from the convalescent patients may be 3 wk after the illness onset, and routine inactivation of plasma should be performed for elimination of potential existing virus. The optimal dose of CP can be calculated based on an empirical formula: volume (liters) = weight of the recipient (kilograms) × the antibody titer of CP.

86. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A, Bander J, Sanky C, Dupper A, Zheng A, Altman DR, Chen BK, Krammer F, Rao Mendu D, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM. Convalescent plasma treatment of severe COVID-19: A matched control study. medRXiv preprint. Published initially on 2020 September 15 as a medRXiv preprint and subsequently Nature Medicine 2020 November; 26: 1708-1713. https://www.nature.com/articles/s41591-020-1088-9.pdf

Abstract Results Convalescent plasma recipients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% Cl: 0.75~0.98; p=0.028). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p = 0.039). In a covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% Cl: 0.05~0.72); p = 0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752).

Mr. President: What the abstract results above mean is that if the patients require intubation (at the end of the Cytokine Cascade and Bradykinin Storm), then there was no survival advantage to *Passive Immunization* with COVID-19 Convalescent Plasma.--***BUT,*** if COVID-19 Convalescent Plasma was given before intubation, in all analyses in this study, there was a significant survival advantage (i.e.: all p values were < 0.05).

87. Fara A, Miltrev Z, Rosalia RA, Assas BM: Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. The Royal Society publishing – Open Biology. 2020 Sep 23; 10(9): 200160. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7536084/

88. Parshley L: This theory might explain “Covid toes” and other mysteries of the disease. Vox. 2020 September 19 https://www.vox.com/21445038/covid-19-symptoms-treatments-bradykinin-cytokine-storm

89. Fajgenbaum DC: Cytokine storm. N Engl J Med 2020; 383: 2255 – 2273. https://www.nejm.org/doi/pdf/10.1056/NEJMra2026131?articleTools=true

90. Karamyan VT: Between two storms, vasoactive peptides or bradykinin underlie severity of COVID-19? The Physiological Society, Physiological Reports REVIEW. 09 March 2021;9 (5):e14796, 1-9. https://physoc.onlinelibrary.wiley.com/doi/10.14814/phy2.14796

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a world-wide pandemic with overwhelming socioeconomic impact. Since inflammation is one of the major causes of COVID-19 complications, the associated molecular mechanisms have been the focus of many studies to better understand this disease and develop improved treatments for patients contracting SARS-CoV-2. Among these, strong emphasis has been placed on pro-inflammatory cytokines, associating severity of COVID-19 with so-called “cytokine storm.” More recently, peptide bradykinin, its dysregulated signaling or “bradykinin storm,” has emerged as a primary mechanism to explain COVID-19-related complications. Unfortunately, this important development may not fully capture the main molecular players that underlie the disease severity. To this end, in this focused review, several lines of evidence are provided to suggest that in addition to bradykinin, two closely related vasoactive peptides, substance P and neurotensin, are also likely to drive microvascular permeability and inflammation, and be responsible for development of COVID-19 pathology. Furthermore, based on published experimental observations, it is postulated that in addition to ACE and neprilysin, peptidase neurolysin (Nln) is also likely to contribute to accumulation of bradykinin, substance P and neurotensin, and progression of the disease. In conclusion, it is proposed that “vasoactive peptide storm” may underlie severity of COVID-19 and that simultaneous inhibition of all three peptidergic systems could be therapeutically more advantageous rather than modulation of any single mechanism alone.

91. Odeh NH: Roles of a bradykinin storm and a cytokine storm in Covid-19 cases. DigitalCommons--@WayneState-- 2021 August 9 https://digitalcommons.wayne.edu/cgi/viewcontent.cgi?article=1075&context=honorstheses

92. Andrus CH: Thank you letter to Gilead Sciences for providing the reference regarding the date of completion of Phase 1 remdesivir trial. 2022 February 16

From: Charles.Andrus@va.gov,
To: Public_affairs@gilead.com,
Cc: Charles.Andrus@va.gov, candrus600@aol.com, Anthony.Fauci@nih.hhs.gov, kara.harris@nih.hhs.gov, Janet.Woodcock@fda.hhs.gov, Denise.Hinton@hhs.gov, Jacqueline.OShaughnessy@fda.hhs.gov, michael.hogan@va.gov,
Subject: RE: Phase 1 remdesivir trial result
Date: Wed, Feb 16, 2022 3:25 pm
Attachments: 3 Andrus SLU cv 8_11_2021.docx (7964K),

2/16/2022

NIAID Case #12276

0.

Dear Gilead:

Thank you for forwarding this article to me: Humeniuk R, Mathias A, Huyen C, Osinusi A, Shen G, Chng E, Ling J, Wu A, German P: Safety, Tolerability, and Tolerability, and Pharmacokinetic of Remdesivir, An antiviral for Treatment of COVID-19, in Healthy Subjects. Clin Transl Sci 2020; 13, 896-906: Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID 19, in Healthy Subjects (wiley.com). I have attached a copy of my CV so you know who I am. Over my decades of involvement with the Veterans Health Administration (VHA), U.S. Department of Veterans, I have attempted to be an advocate for each and every individual Veteran patient that presented to me. My biggest challenge was to have the phrase in VHA Handbook 1400.1 on Resident Supervision revised (after ~50 years): **Level 3: Attending Surgeon not present, immediately available.** What was condoned by the inappropriate application of Level 3 was that on nights, weekends, holidays, family get togethers, etc., some University Attending Surgeons would staff residents in the OR from afar (ghost surgery). Twenty years ago, I fought for that change all the way to the U.S. Court of Appeals for the Federal Circuit in *Andrus v VA*, Case 03-3162—in which the court *per curium* "failed to rule." I lost all my battles with the VA; but, in the end, all Attending Surgeons-of-Record in the VA today are required to be present in the OR suite during every individual Veterans' operation which is definitely to the betterment of every Veteran patient. The VA saved face by: 1.) changing VAH Handbook from 1400.1 to VAH Handbook 1400.01 so you can't find previous versions electronically if you don't know the previous URL.; 2.) as is common practice today, in the agencies of the Executive Branch of the Federal Government, electronically overwrite documents without designating what has been rescinded or that there was even a previous document; and 3.) I became and still am an *unperson* in the VA from 4/1982-8/2016 since my Official Personnel File (OPF) has been misplaced/lost. Thus, from April 1982 to August 2016, I don't exist in the VA until I returned in August 2016, as an Attending Physician and General Surgeon at the St. Louis VAMC. My VA service from 1982 to 2002 does not exist "officially" even though from 8/1996 to 1/2002, I was the Chief of Surgery, Edward Hines, Jr. VAH (the first hospital of the University-VA affiliation in 1946 under PL-79-293); and I was interviewed for the position of Under Secretary for Health

(USH) of the Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (DVA) on the 10th floor of VACO (across Lafyette Square from *The White House*) on the afternoon of December 10, 1999. I am telling you this, so I can put in context for you the convoluted process regarding Remdesivir that parallels that which occurred to me in my fight to stop Physically Unsupervised resident surgeons by VA misdirection and obfuscation twenty years ago. Today, by changing URLs, electronic overwriting, and semantics, the FDA, the NIH, the CDC, the VA, etc. have somewhat stretched the truth before the American people.

I thank you for forwarding the reference regarding the Phase I studies completed for Remdesivir (RDV). As is quoted in the article:

On May 1, 2020, based on available data from to global clinical trials, the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-19 Based on these clinical data, RDV has been approved for the treatment of adults and pediatric patients in Japan. This paper describes the safety and pharmacokinetics (PKs) of the solution and lyophilized formulations of i.v. RDV administered to healthy participants in the two first-in-human (FIH) phase I studies.

The above paragraph suggests that the FDA issued the EUA after review of the two first-in-human phase I studies involving Remdesivir (VEKLURY) and that review occurred at least by May 1, 2020, which means that phase I human trials were deemed safe and implies that the phase I trials *de facto* were completed—BUT, that presented multiple ethical and legal dilemmas for the FDA, the NIH, etc.

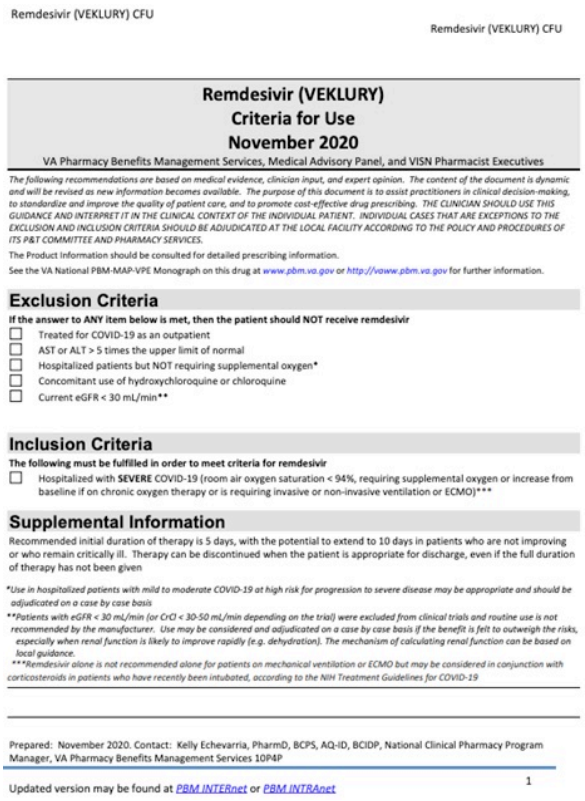
1. The FDA issued the first Remdesivir EUA on May 1, 2020 (which was the date when Dr. Fauci announced Remdesivir from the Oval Office); yet by making it an EUA, Remdesivir,-- the FDA was defining Remdesivir as an "unapproved" drug in the treatment of COVID-19

2. As phase II/III clinical trials proceeded, prospective participants who had contracted COVID-19 should have been made aware in their Informed Consent that with The Right to Try Act, PL-115-176 that they could still be afforded Remdesivir by non-participation in the mandated RCT placebo trials—for that matter, all of America should have been told of this by the FDA! As the Phase I studies *de facto* were completed, any American could have asked for Remdesivir under PL-115-176 and should have received it!

3. As I am sure that you are well-aware that Remdesivir is "a single diastereomeric monophoramidate prodrug that inhibits viral RNA polymerases" which works best during the initial viremic phase of COVID-19—rather than in the later severe disease phases of cytokine cascade and bradykinin storm. Unfortunately, with the issuance of the EUA on May 1, 2020, "the US Food and Drug Administration **(FDA) granted emergency use authorization** to allow RDV to treat adults and children **hospitalized with severe COVID-19**." In fact, the **FDA removed the severity stipulation quietly**--not notifying the American public of this significant retraction--on **August 28, 2020**. In the FDA January 21, 2022 letter to Madelyn Low, MBS, Manager, Regulatory Affairs, Gilead Sciences, Inc., https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fda-authorization-letter.pdf?la=en&hash=FD3737583BE0E4DF710ADB36AEAA2DBD, there are 8 references on pages 1 and 2 in which the Acting Chief Scientist of FDA outlined the chronology regarding Remdesivir including the August 28, 2020 retraction of the severity of illness stipulation: "...FDA revised authorized use of Veklury to no longer limit its use for the treatment of patients with severe disease." (How could Remdesivir being an "unapproved" drug in the treatment of COVID-19 under the FDA's EUAs standards become a drug that the FDA was officially revising authorization so it could be given early in the course of the disease? It seems like a bunch of semantics; but if that bunch of semantics limits the rights of individuals in America, that is wrong.

4. "On October 22, 2020, FDA also approved NDA 214787 for Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 Kg) **requiring hospitalization."** At this point, Remdesivir (VEKLURY) was designated by the FDA as a prescription drug (NDA 214787) on October 22, 2020.

5. In November 2020, the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs issued for the fully-FDA- authorized-prescription drug, VEKLURY, NDA 214787 the: "Remdesivir (VEKLURY) Criteria for Use" of how to administer Remdesivir with the severity Inclusion Criteria exclusively included that had been removed previously on August 28, 2020 by the FDA:



Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY)
Criteria for Use
November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive remdesivir

- ☐ Treated for COVID-19 as an outpatient
- ☐ AST or ALT > 5 times the upper limit of normal
- ☐ Hospitalized patients but NOT requiring supplemental oxygen*
- ☐ Concomitant use of hydroxychloroquine or chloroquine
- ☐ Current eGFR < 30 mL/min**

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

- ☐ Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

Supplemental Information

Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given

**Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis*

***Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.*

****Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19*

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

Updated version may be found at PBM INTERnet or PBM INTRAnet

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6. When I had a patient denied Remdesivir by the Infectious Diseases service quoting the November VA directive, I contacted Richard Stone, M.D., VHA Chief Medical Executive (the Trump Administration's title for the Under Secretary for Health, VHA, DVA). Dr. Stone contacted VA Pharmacy Management Services and the Medical Advisory Board. At first, the VA responded to me. But when the VA became evasive, I contacted the FDA, the NIAID (Case #12276), and wrote a letter to the editors of the *The New England Journal of Medicine*. None responded to me.

7. I recently had a patient admitted to the Surgical Service who had newly turned COVID-19 positive (less than 24 hours from negative to positive). The recommendations from the same Infectious Diseases service was that if the patient had any symptomatology like headache or neck pain, give three days of Remdesivir; and if the patient develops a cough, give five days of Remdesivir and dexamethasone. By the time of that consult, the CDC had stated a month before that Regeneron's and Eli Lilly's monoclonal cocktails were ineffective against COVID-19, omicron variant; and, thus, GlaxoSmithKline's *sotrovimab* was and is being *de facto* rationed at present time.

Once again, I thank all involved in addressing my question at Gilead regarding if a phase I study had been completed in the case of Remdesivir. You were all very professional and willing to listen—and, most of all, my personal thanks as a Federal Physician and Surgeon for you have provided this information which may become an outstanding service for the people of the United States of America.

Thank you,
Charles Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine

Chief and Attending General Surgeon, Unit II (SLU) General Surgery division, Surgical Service, John Cochran (112JC), St. Louis, MO 63106

Office phone: 314-652-4100 ext 54463 Beeper: 314-491-2417
Home phone: 314-455-9482

P.S. I hope this e-mail will initiate an overall discussion regarding transparency by the agencies of the U.S. Government in regards to the EARLY (< 72 hours from diagnosis) administration with intent of synergism of COVID-19 Convalescent Plasma, COVID-19 monoclonal antibodies, Remdesivir and other future antivirals, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.

From: Public Affairs <Public_affairs@gilead.com>
Sent: Wednesday, February 16, 2022 7:54 AM
To: Andrus, Charles H. (STL) <Charles.Andrus@va.gov>
Subject: [EXTERNAL] Phase 1 remdesivir trial results

Dr. Andrus, You can find the published results of the Phase 1 remdesivir trial here: https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.12840

Thank you for your inquiry,

Gilead Public Affairs

93. 2020-04-07 Bloch EM, Shoham S, Casadevall A, Sachals BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JR, A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski L, Bailey JA, Tobian AAR: Deployment of convalescent plasma for the prevention and treatment of COVID-19. https://www.jci.org/articles/view/138745 or .pdf version: https://www.jci.org/articles/view/138745/pdf

94. 2020-05-14 Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Buskirk CMV, Winters JL, Stubbs JR, Paneth NS, Casadevall A: Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. Med$R_x$iv – Preprint May 12, 2020. https://web.archive.org/web/20200515045004/https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1.full.pdf

95. 2020-06-03 Casadevall A, Joyner MJ, Pirosfki LA: A randomized trial of convalescent plasma for COVID-19 -- Potentially hopeful signals. JAMA. June 3, 2020: E1 – E3. https://pubmed.ncbi.nlm.nih.gov/32492105/ ; August 4, 2020; 324 (5): 455-457. https://jamanetwork.com/journals/jama/fullarticle/2766940

96. 2020-07-07 Casadevall A, Joyner MJ, Pirofski LA: SARS-CoV-2 viral load and antibody responses: the case for convalescent plasma therapy. J Clinical Investigation 2020 Jul 7; 130 (10): 5112-5114. https://www.jci.org/articles/view/139760/pdf

97. 2020-07-19 Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, Wiggins CC, Senefeld JW, Klompas AM, Hodge DO, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimabal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Soto JCD, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS. COVID-19 Convalescent Plasma in 20,000 hospitalized patients. Mayo Clin Proc September 2020; 95(9): 1888-1897. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7368917/pdf/main.pdf

98. 2020-08-12 Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Soto JCD, Baker SE, Shepherd JRA, van Helmond N, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whenlan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL, Wright RS, Carter RE, Casadevall A: Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience. Version 1. medRxiv Preprint. 2020 Aug 12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430623/?report=printable

99. 2021-01-13 Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea FR, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather D, Wright RS, Casadevall A, *et. al.*: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med, January 13, 2021, at NEJM.org; then republished N Engl J Med 2021; 384:1015-1027. https://www.nejm.org/doi/full/10.1056/NEJMoa2031893

100. 2021-03-18 Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiffins CC, Bruno KA, Klompas AM, Lesseer ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL: Wright RS, Casadevall A: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021 Mar 18; 384 (11): https://www.nejm.org/doi/full/10.1056/nejmoa2031893 and https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031893?articleTools=true

101. 2021-05 Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, Grossman BJ, Henderson JP, Musser J, Salazar E, Hartman WR, Bouvier NM, Liu

STH, Pirofski LA, Baker SE, van Helmond N, Wright TS, Fairweather D, Bruno KA, Wang Z, Paneth NS, Casadevall A, Joyner M: The effect of convalescent plasma therapy on COVID-19 patient mortality: Systematic review and meta-analysis. Mayo Clin Proc, 2021 May; 96 (5): 1262-1275.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7888247/pdf/main.pdf

> … Importantly, many of the patients enrolled in the studies included in the analyses received convalescent plasma transfusions later in their disease course. In this context, before antibiotics and effective vaccinations, convalescent plasma therapy was widely understood to be most efficacious very early in the course of hospitalizations.[2, 155] As a result, our analysis may underestimate the mortality reduction achievable through early administration of high-titer convalescent plasma for COVID-19.
>
> **Conclusion**
> This real-time systematic review and meta-analysis of contemporaneous studies highlights that the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19 and suggests that **early transfusion of high-titer plasma represents the optimal use scenario to reduce the risk of mortality among patients with COVID-19**. These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent.

102. 2021-06-04 Casadevall A, Dragotakes Q, Johnson PW, Senefeld JW, Klassen SA, Wright RS, Joyner MJ, Paneth N, Carter RE: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. eLife 2021; 10e69866.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205484/pdf/elife-69866.pdf

> **Abstract:** ***(Extremely Important!)***
> …Changes in the number of hospital admissions, SARS-CoV-2 variants, and age of patients could not explain these findings. The retreat from CCP might have resulted in as many as 29,000 excess deaths from mid-November 2020 to February 2021.
> **Conclusions:** A strong inverse correlation between CCP use and mortality per admission in the USA provides population-level evidence consistent with the notion that CCP reduces mortality in COVID-19 and suggests that the recent decline in usage could have resulted in excess deaths.

103. 2021-12-20 Senefeld JW, Johnson PW, Kunze KL, Bloch EM, van Helmond N, Golafshar MA, Klassen SA, Klompas AM, Sexton MA, Diaz Soto JC, Grossman BJ, Tobian AAR, Goel R, Wiggins JL, Casadevall A, Paneth NS, Shaz BH, Petersen MM, Sachais BS, Buras MR, Wieczorek MA, Russoniello B, Dumont LJ, Baker SE, Vassallo RR, Shepherd JRA, Young PP, Verdun NC, Marks P, Haley NR, Rea RF, Katz L, Herasevich V, Waxman DA, Whelan ER, Bergman A, Clayburn AJ, Grabowski MK, Larson KF, Ripoll JG, Andersen KJ, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Buchholtz ZA, Pletsch MC, Wright K, Greenshields JT, Joyner MJ, Wright RS, Carter RE, Fairweather D: Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study. PLOS Medicine 2021 December 20.
https://pmc.ncbi.nlm.nih.gov/articles/PMC8730442/pdf/pmed.1003872.pdf

104. 2022-02 Paneth N, Casadevall A, Pirofski L, Henderson JP, Grossman BJ, Shoham S, Joyner MJ: WHO covid-19 drugs guideline: reconsider using convalescent plasma. BMJ 2022 February; 376: o295. https://www.bmj.com/content/376/bmj.o295

105. 2022-03-07 Casadevall A, Grossman BJ, Joyner MJ, Henderson JP, Paneth N, Pirofski LA, Shoham S: National COVID-19 Convalescent Plasma Project. Last digitized for International Archive, March 7, 2022. https://ccpp19.org/about/index.html which can no longer be found on the Internet but using the Wayback Machine, 152 captures are noted with the first capture being April 1, 2020.

106. CDC: The U.S. Public Health Service untreated syphilis study at Tuskegee. The untreated syphilis study at Tuskegee timeline. https://www.cdc.gov/tuskegee/about/timeline.html?CDC_AAref_Val=https://www.cdc.gov/tuskegee/timeline.htm

107. CDC: The Public Health Service untreated syphilis study at Tuskegee Timeline. https://www.cdc.gov/tuskegee/index.html

108. Clinton B: Remarks by the President in apology for study done in Tuskegee. *The White House*, Office of the Press Secretary, 1997 May 16. https://clintonwhitehouse4.archives.gov/textonly/New/Remarks/Fri/19970516-898.html

109. **YouTube: Regeneron's Leonard S. Schleifer meets with Trump at the White House, 3/2/2020. https://www.youtube.com/watch?v=31i6p_stzW8 AT THIS MEETING, PRESIDENT TRUMP AND ALL THE PEOPLE OF THE WORLD WERE MISLED BY OMISSION / MISREPRESENTING THE DISTINCTION BETWEEN *ACTIVE IMMUNIZATION (vaccines)* versus *PASSIVE IMMUNIZATION (convalescent plasma, convalescent sera, monoclonal antibodies, monoclonal antibody cocktail, etc.)*.** The cost of production of a dose (1/2 unit of fresh frozen plasma) COVID-19 Convalescent Plasma (CCP) which was available in March 2020 is ~$200 while a dose of REGEN-COV™ (Casirivimab with imdevimab) which would be several months into the future and would cost ~$3000 a dose. A monoclonal antibody is specific for one antigen (e.g. a specific site on the spike point) and is likely to be ineffective on future variants like Omicron. Polyclonal antibodies like Convalescent Plasma will have multiple antibodies of such sites as on the spike protein and will be available as the SARS-CoV-2 mutates. (e.g. more effective on the Omicron variant).

******* Full 56:54 minute meeting in *The White House* where they went around the table introducing the key players: https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus with the complete transcript: https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/** This **linchpin** *White House* meeting included CEOs, presidents, and Medical Directors of the major biomedical and pharmaceutical companies who could provide vaccines, monoclonal antibodies, and antivirals; the Secretary of the U.S. Department of Health and Human Services and its agencies (e.g.: FDA, NIH, CDC, etc.); and the Vice-president and the President of the United States of American. 1.) Nobody defined the foundational basics of Clinical Immunology: Active Immunization and Passive Immunization. 2.) Everything was in Generalities – NOT THE INDIVIDUAL PATIENT! 3.) The not-for-profit American

Red Cross was *NOT* officially invited "to the table" until July 30, 2020—by that time, the U.S.A. had gone so far down the Rabbit Hole, they did not know how to get out! 4.) No physician in that room, on that day, has probably cared for the individual patient since Medical School.

Individuals at the White House meeting of March 2, 2020.

President Donald Trump, 2 years Fordham University and the 2 years Wharton School of the University of Pennsylvania, B.S. in Economics

Alexander Azar, Secretary of the U.S. Department of Health and Human Services, summa cum laude in government and economics from Dartmouth and J.D. from Yale University

Emma Walmsley , CEO of GlaxoSmithKline, MA in Classics and Modern Languages from Oxford University (Christ Church)

Anthony Fauci, M.D., Director of the NIAID of the NIH, College of the Holy Cross with a BA in classics and a MD from Cornell University graduating 1st in his class

Robert Redfield, M.D., Director of the CDC, graduated from Georgetown University's College of Arts and Sciences with a BS and MD from Georgetown University School of Medicine

Daniel Menichella, CEO of CureVac, BA in economics from Harvard University and a MBA from University of North Carolina at Chapel Hill

John Shiver,PhD, Senior Vice President, Vaccines Global R&D at Sanofi Vaccines, BS in Chemistry/Mathematics, Woffard College and a PhD in Chemistry from the University of Florida

Leonard Schleifer, M.D., PhD, CEO Regeneron, BS at Cornell University and an MD-PhD from the University of Virginia

Stephane Bancel, CEO of Moderna, masters degrees from both CentraleSupélec of Paris-Saclay University (engineering) and the University of Minnesota (biological engineering) and an MBA from Harvard Business School

Daniel O'Day, BS, MBA, Chairman and CEO of Gilead Sciences has a BS in biology from Georgetown University and an MBA from Columbia University in New York

Steven Hahn, M.D., Commissioner, U.S. Food and Drug Administration, BA in Biology from Rice University and MD from Temple University

Mikael Dolsten, M.D., Ph.D., Chief Scientific Officer of Pfizer, Ph.D. in tumor immunology and a MD from Lund University

Joseph Kim, Ph.D., Inovio Pharmaceuticals, BS degrees in Chemical Engineering and Economics from MIT, a Ph.D. in immunology from the University of Pennsylvania, and an MBA in finance from the Wharton School of Business, University of Pennsylvania

Paul Stoffels, M.D., Chief Scientific Officer of Johnson & Johnson, studied medicine at the University of Diepenbeek and the University of Antwerp in Belgium and Infectious Diseases and Tropical Medicine at the Institute of Tropical Medicine in Antwerp, Belgium.

Anne Schuchat, M.D., Principal Deputy Director of the CDC, Swarthmore College and MD Dartmouth Medical School

Stanley Erck, President and CEO of Novavax, undergraduate degree from the University of Illinois and MBA in economics and finance from the Booth School of Business, The University of Chicago

Ambassador Deborah Birx, M.D., U.S. Department of State, BS in chemistry from Houghton College and MD from Pennsylvania State University.

110. 2020-07-30 American Red Cross: President Trump visits the American Red Cross. To highlight need for convalescent plasma during COVID-19. https://www.redcross.org/about-us/news-and-events/press-release/2020/red-cross-highlights-need-for-convalescent-plasma-during-covid-19.html

111. 2020-07-30 Hahn S: Plasma Donation – PSA. (*Appeal by the FDA Commissioner on the same day as the American Red Cross visit by President Trump soliciting patients recovering from COVID-19 to donate COVID-19 Convalescent Plasma.)* https://www.youtube.com/watch?v=PlX15rWdBbY

112. 2020-08-23 Trump D: Donald Trump August 23 White House COVID-19 Press Conference Transcript. Rev Aug 23, 2020. Video of the conference: https://www.youtube.com/watch?v=nE0EkrElCRk Transcript: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

Appendix 1 of a draft cover letter (never sent) to the President Biden of August 2021:

Transcript of August 23, 2021 White House press conference in its entirety: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

(The video of the August 23, 2020 White House press conference in its entirety: https://www.youtube.com/watch?v=nE0EkrElCRk)

President Donald Trump held an August 23 coronavirus press conference where he announced the FDA is issuing an emergency authorization for a COVID-19 treatment called convalescent plasma. Trump touted the approval as a "historic announcement." Read the full transcript of the press conference here.

Donald Trump: (01:38)
Thank you very much, and it's good to see you all. Hope you had a great weekend at your convention. We're going to have a great convention coming up, and I look forward to it.

Donald Trump: (01:51)
But before I discuss a very historic breakthrough in our fight against the China virus, I'd like to provide an update on the recent wildfires in California and the storms in the Gulf of Mexico. Yesterday, I approved a major disaster declaration for California, spoke to Governor Newsom as they battled two of the worst wildfires in the history of their state. That continues.

Donald Trump: (02:19)
The federal government has already deployed over 26,000 first responders and personnel to battle the wildfires. We're working very closely with the Governor and very closely with a

lot of great state representatives and local representatives. We'll take care of the situation, but we have 26,000 first responders already. Our hearts go out to the thousands of families who have lost their homes, as we grieve for the families of two first responders and five residents who have tragically lost their lives in a very horrific fire, one of the biggest we've ever seen.

Donald Trump: (03:01)
My administration is also closely monitoring Hurricane Marco and Tropical Storm Laura, which are coming in rapidly. Hurricane Marco is expected to make landfall in Louisiana tomorrow, and Tropical Storm Laura is expected to hit Louisiana two days later. This is somewhat unprecedented, the scope of the storms, and also the fact that they come so quickly after one another. Both storms have the potential of gathering strength before they make landfall and could cause significant damage across the Gulf Coast and also in Puerto Rico. We have everybody stationed and ready to go in Puerto Rico and the Gulf Coast. We have tremendous, tremendous people. FEMA is lined up. We have the Coast Guard ready. The Coast Guard has done a fantastic job. They do such good work, and we want to thank our great Coast Guard.

Donald Trump: (03:58)
I'm asking all Americans in the storm's path to follow the instructions of your state and local governments very closely. I've approved emergency declarations for Puerto Rico and for Louisiana. FEMA is mobilized on the ground and is ready to help. They will be in there very quickly, very, very quickly. I spoke to Governor John Bel Edwards also of Louisiana, and I've informed him, and at his request also, a major disaster declaration is signed and ready to go. We have everybody ready in Puerto Rico, the Gulf Coast, Louisiana, and also on the forest fires in California. We have a great team. Unfortunately, we have some very, very powerful natural disasters.

Donald Trump: (04:47)
On the therapeutics front, this is what I've been looking to do for a long time. This is a great thing. Today, I'm pleased to make a truly historic announcement in our battle against the China virus that will save countless lives. The FDA has issued an Emergency Use Authorization, and a that's such a powerful term, Emergency Use Authorization, for a treatment known as convalescent plasma. This is a powerful therapy that transfuses very, very strong antibodies from the blood of recovered patients to help treat patients battling a current infection. It's had an incredible rate of success. Today's action will dramatically expand access to this treatment.

Donald Trump: (05:39)
I want to thank Dr. Hahn and Secretary Azar. I want to thank the FDA, all of the people that have been working very hard on this. It showed tremendous potential. It's only made possible because of Operation Warp Speed. That is everybody working together. We're years ahead of approvals that we would be if we went by the speed levels of past administration. We'd be two years, three years behind where we are today, and that includes on vaccines that you'll be hearing about very soon, very shortly.

Donald Trump: (06:16)
To deliver treatments and vaccine to save lives, we're removing unnecessary barriers and delays, not by cutting corners, but by marshaling the full power of the federal government. We provided $48 million to fund the Mayo Clinic study that tested the efficacy of convalescent plasma for patients with the virus. Through this study over 100,000 Americans have already enrolled to receive this treatment, and it is proven to reduce mortality by 35%. It's a tremendous number. The FDA, MIT, Harvard, and Mount Sinai Hospital have also found convalescent plasma to be a very effective method of fighting this horrible disease. Based on the science and the data, the FDA has made the independent determination that the treatment is safe and very effective.

Donald Trump: (07:12)
Recently, we provided up to $270 million to the American Red Cross and America's blood centers to support the collection of up to 360,000 units of plasma. In late July, we launched a

nationwide campaign to ask patients who have recovered, and these are patients that have been incredible the way they've donated. But these are people recovered from the virus to donate plasma. Since then, weekly plasma donations have doubled. Today, I once again urge all Americans who have recovered from the virus to go to coronavirus.gov and sign up and donate plasma today, please. It's been really an incredible … Just incredible people. The country has united so strongly behind this.

Donald Trump: (08:08)
I'll go over the numbers, but if you look at what's happened and the success that we've had that people don't talk about, the United States has experienced the lowest case fatality rate of any major country in the world. You don't hear that. The European Union's case fatality rate is estimated to be three times higher than that in the United States. Europe has seen 33% more fatalities compared to a typical non-pandemic year than the United States.

Donald Trump: (08:38)
I just want to ask two of our people that have done such a fantastic job, Alex Azar and Stephen Hahn to say a few words. Stephen, I want to thank you because the FDA really stepped up and especially over the last few days in getting this done. The results have been incredible, and I think you'll see the results even go up very substantially. So we appreciate it. And maybe I'll ask Alex to go first, and then Stephen. Thank you very much, Alex.

Alex Azar: (09:06)
Well, thank you very much, Mr. President. Thanks for the bold leadership that allowed us to deliver this very happy news today. Thanks to your all-of-America approach, America has done more than any other country to expand the arsenal that we have to battle COVID-19. Thanks to early efforts by your administration, Americans have broader access to these treatments, including convalescent plasma, than patients anywhere else in the world.

Alex Azar: (09:33)
In early April, early in our fight against COVID-19, the FDA, BARDA, the Mayo Clinic, and other partners sprang into action to set up an expanded access protocol for this promising treatment. President Trump is the right-to-try President, and he's fought hard to ensure that Americans can have access to promising COVID-19 treatments. Convalescent plasma has been a tried-and-true therapeutic method in prior outbreaks, but the President wanted to ensure that we develop the data to support its use. This FDA authorization is one result of that effort.

Alex Azar: (10:06)
The data we gathered suggests that patients who were treated early in their disease course, within three days of being diagnosed with plasma containing high levels of antibodies, benefited the most from treatment. We saw about a 35% better survival in the patients who benefited most from the treatment, which were patients under 80, who were not on artificial respiration. I just want to emphasize this point because I don't want you to gloss over this number. We dream in drug development of something like a 35% mortality reduction. This is a major advance in the treatment of patients. This is a major advance.

Alex Azar: (10:51)
Convalescent plasma is one new tool that we've added to our arsenal against COVID-19 alongside remdesivir, steroids, and a number of other promising options currently being studied. Because of the President's Operation Warp Speed, we expect to have other new results and new options reaching patients as soon as this fall. Operation Warp Speed is supporting experimental therapeutics all the way through to manufacturing, so that if they meet FDA's gold standard for safety and efficacy, they can begin reaching patients without a day wasted.

Alex Azar: (11:24)
Americans who have tested positive for and recovered from COVID-19 can go to coronavirus.gov to find out a quick, convenient way to play a potentially lifesaving role in

our fight. Know if you donate plasma, you could save a life. We've also provided guidance, so healthcare providers can contact patients who have recovered from COVID-19 and give them information on how they can donate.

Alex Azar: (11:48)
So thank you again, Mr. President for supporting this remarkable progress against COVID-19, and I want to thank Dr. Hahn, Dr. Marks, and the entire team at the FDA for the speed with which they've approached this, the diligence to ensure that this meets the standards at FDA. I'll turn it over to Dr. Hahn, if it's okay, Mr. President.

Donald Trump: (12:07)
[crosstalk 00:12:07] thank you very much. Please, Doctor?

Dr. Hahn: (12:09)
Thank you, Mr. President-

Donald Trump: (12:10)
[crosstalk 00:12:10].

Dr. Hahn: (12:10)
… for your leadership. It's good to be here today to announce FDA's recent decision. From the beginning of this pandemic, the President has asked FDA to cut back red tape to try to speed medical products into the hands of providers, patients, and American consumers. I just want to echo the President's thanks to the more than the 17,000 men and women who work at FDA. They have worked day and night to, in fact, do that.

Dr. Hahn: (12:36)
Plasma is the liquid portion of the blood. That liquid portion contains the natural immunity that someone develops in response to an infection, in this case COVID-19. That liquid portion can be extracted. And for many years, as the President and Secretary Azar said, has been given to patients with infectious diseases for more than a hundred years. So there was a really good rationale for why this might work. In fact, as was mentioned, in early April, an expanded access program was started at the Mayo Clinic with the support of the federal government under President Trump's leadership. That has gone on for the last four months. More than 90,000, close to 100,000, Americans have enrolled in this program, and over 70,000 have received treatment. This is one of the largest expanded access programs in the history of FDA. So a very successful approach to evaluating how convalescent plasma would work.

Dr. Hahn: (13:34)
In the independent judgment of experts and expert scientists at FDA who have reviewed the totality of data, not just the data from this expanded access program, but more than a dozen published studies, as well as the historical experience associated with this, those scientists have concluded that COVID-19 convalescent plasma is safe and shows promising efficacy, thereby meeting the criteria for an emergency use authorization. In the optimal patients, as described by secretary Azar, treated with convalescent plasma at the highest titers, there was a 35% improvement in survival, which is a significant clinical benefit. Now, we're waiting for more data. We're going to continue to gather data, but this clearly meets the criteria that we've established for emergency use authorization, and we're very pleased with these results.

Dr. Hahn: (14:27)
Let me just put this in perspective. Many of you know I was a cancer doctor before I became FDA commissioner, and a 35% improvement in survival is a pretty substantial clinical benefit. What that means is, and if the data continue to pan out, 100 people who are sick with COVID-19, 35 would have been saved because of the administration of plasma. We've seen a great deal of demand for this from doctors around the country. What this emergency use authorization today does, it allows us to continue that and meet the demand.

Dr. Hahn: (15:00)
Again, I want to echo the President's and the Secretary's ask of the American people. If

you've recovered from COVID-19, please donate. It could save a life. Mr. President, thank you again.

Donald Trump: (15:11)
Thank you very much, Stephen. I appreciate it.

Speaker 6: (15:18)
Mr. President?

Donald Trump: (15:19)
Okay, any questions?

Speaker 6: (15:19)
Mr. President? Mr. President?

Speaker 7: (15:19)
Thank you, Mr. President. I want to first ask you about the COVID-19 drugs that are in phase three.

Donald Trump: (15:23)
[crosstalk 00:15:24].

Speaker 7: (15:24)
Are they going to be available to the American population on … You and I talked previously about this idea of right to try.

Donald Trump: (15:32)
Right.

Speaker 7: (15:33)
Can we assure the American people that if it's being studied and it's in phase three, you have that right?

Donald Trump: (15:38)
That's a great question, and I'm not sure a lot of people have been thinking about right to try. We're all waiting for the final answer. Maybe I could ask Stephen, but I would say that right to try is exactly … If somebody is virtually terminal, in other words they're not going to make it, and if we have these incredible therapies and drugs that are happening, Alex, I think it's a very interesting question. I congratulate you for that question because I think we're-

Speaker 7: (16:05)
Thanks, Mr. President.

Donald Trump: (16:05)
… all waiting for that exact final endpoint. What about that, Stephen? We have all of these seemingly great answers that are ready to come out, but because of the process, it takes a little- Can we use some of this early under Right to Try? Please.

Dr. Hahn: (16:18)
So it's a really good question. Of course, it all depends on the clinical circumstances and what a doctor and a patient together decide with respect to the administration of any agent.

Dr. Hahn: (16:29)

But if you think about what happened with convalescent plasma and the expanded access program, this is exactly what happened. We have ongoing clinical trials that are randomized between placebo or an inactive substance and the convalescent plasma. While that was going on, we knew that there was great demand from patients and doctors. The expanded access program is a way of actually doing that and fits perfectly with what the President just said about allowing people to be able to use something that **we have now determined to be very safe.**

Donald Trump: (16:57)
I think it was something we have to really consider very strongly.

Dr. Hahn: (17:00)
Yes, sir.

Donald Trump: (17:00)
I think it's fantastic. You should get credit for that.

Speaker 7: (17:04)
Thanks, Mr. President.

Donald Trump: (17:04)
Thank you. That's very good.

Speaker 8: (17:04)
Mr. President?

Donald Trump: (17:04)
Please, in the back. [OEN 00:17:08]?

Speaker 9: (17:10)
Thank you Mr. President. Convalescent plasma as a treatment has been around for nearly a hundred years. You mentioned Operation Warp Speed, which enabled this process to move along a lot faster. What went into the effort for this to be approved for COVID-19? And was that holdup political in nature?

Donald Trump: (17:30)
Well, I think that there might have been a holdup, but we broke the logjam over the last week, to be honest. I think that there are people in the FDA and actually in your larger department that can see things being held up and wouldn't mind so much. That's my opinion, a very strong opinion. And that's for political reasons. This has nothing to do with politics. This has to do with life or death. So we are being very strong, and we are being very forthright. We have got some incredible answers, and we're not going to let them be held up because every day is lives, and we're not going to let that happen. Okay? Very good, thank you.

Speaker 10: (18:06)
Mr. President?

Donald Trump: (18:06)
Please, go ahead.

Speaker 11: (18:10)
Mr. President, in announcing this today, you said that the FDA has made the independent determination that the treatment is **safe** and very effective. Yet Dr Hahn just said it was showing promising efficacy. Which of the two is correct?

Donald Trump: (18:25)
Well, I think I'll let Dr. Hahn answer that question.

Dr. Hahn: (18:29)
Under our legal authority for Emergency Use Authorization, this is not the same as an approval, but it's an authorization, and it allows us to expand the access to this. We know we're going to continue to collect data. We knew that for all of our Emergency Use Authorizations.

Dr. Hahn: (18:44)
So, for example, remdesivir, which was approved or authorized on May 1st, we're still collecting data, and we will continue to do that with plasma as well. So it's the nuances of the language around the authorization that we use and the legal aspect too.

Speaker 11: (18:57)
It's a promising treatment. You couldn't say it's very effective just yet.

Dr. Hahn: (19:02)
If you're one of those 35 out of 100 people who these data suggest or show survive as a result of it, this is pretty significant for that person and their family.

Donald Trump: (19:12)
Okay, this is a very big day. It's a day we've been looking forward to. Thank you very much. Great questions.

Speaker 12: (19:18)
Was there pressure on you, Dr. Hahn, to authorize this?

Speaker 13: (19:18)
Dr. Hahn?

Speaker 14: (19:18)
Mr. President [crosstalk 00:19:19]

Speaker 12: (19:19)
Dr. Hahn. Could you answer that question? [crosstalk 00:19:19] Dr. Hahn, to authorize this.

Speaker 12: (19:21)
(silence)

113. Fauci A: *On Call—A Doctor's Journey in Public Service*. USA: VIKING, Penguin Random House, LLC, 2024. https://www.penguinrandomhouse.com/books/743358/on-call-by-anthony-fauci-md/

114. Hu DJ: On Call: A doctor's journey in public service. Emerg Infect Dis 2024 Dec; 30(12): 2705. https://pmc.ncbi.nlm.nih.gov/articles/PMC11616647/pdf/24-1059.pdf

115. 2020-08-23 Hahn S: Dr. Hahn discussing convalescent plasma at White House News conference. https://www.facebook.com/FDA/videos/dr-hahn-convalescent-plasma-eua/350991072605290/ goes directly to Dr. Hahn - Convalescent Plasma EUA (facebook.com) (https://www.facebook.com/FDA/videos/350991072605290/) Dr. Hahn's words that follow are extremely important because of what resulted:

> By stating that the data was not just from the Mayo Clinic/(FDA) expanded access program as you will note below, Dr. Hahn justified that the issuing of the EUA was completely appropriate. But, in so doing, availability of COVID-19 convalescent plasma from any of the previous Expanded Access Programs was now *de facto* completely suspended / interrupted.

So, in the independent judgment of experts and expert scientists at FDA, who have reviewed the totality of data – not just the data from this expanded access program but more than a dozen published studies as well as the historical experience associated with this – those scientists have concluded that COVID-19 convalescent plasma is safe and shows promising efficacy thereby meeting the criteria for an emergency use authorization.

116. FDA News Release: FDA issues emergency use authorization for Convalescent Plasma as potential promising COVID-19 treatment, another achievement in Administration's fight against pandemic. U.S. Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency's ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this

product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Today's action follows the FDA's extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.
The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:
"The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Secretary Azar. "The Trump Administration recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private partners began work on making this product available across the country while continuing to evaluate data through clinical trials. Our work on convalescent plasma has delivered broader access to the product than is available in any other country and reached more than 70,000 American patients so far. We are deeply grateful to Americans who have already donated and encourage individuals who have recovered from COVID-19 to consider donating convalescent plasma."

Stephen M. Hahn, M.D., FDA Commissioner:
"I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as possible in order to save lives. We're encouraged by the early promising data that we've seen about convalescent plasma. The data from studies conducted this year shows that plasma from patients who've recovered from COVID-19 has the potential to help treat those who are suffering from the effects of getting this terrible virus," said Dr. Hahn. "At the same time, we will continue to work with researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent plasma in treating patients infected with the novel coronavirus."

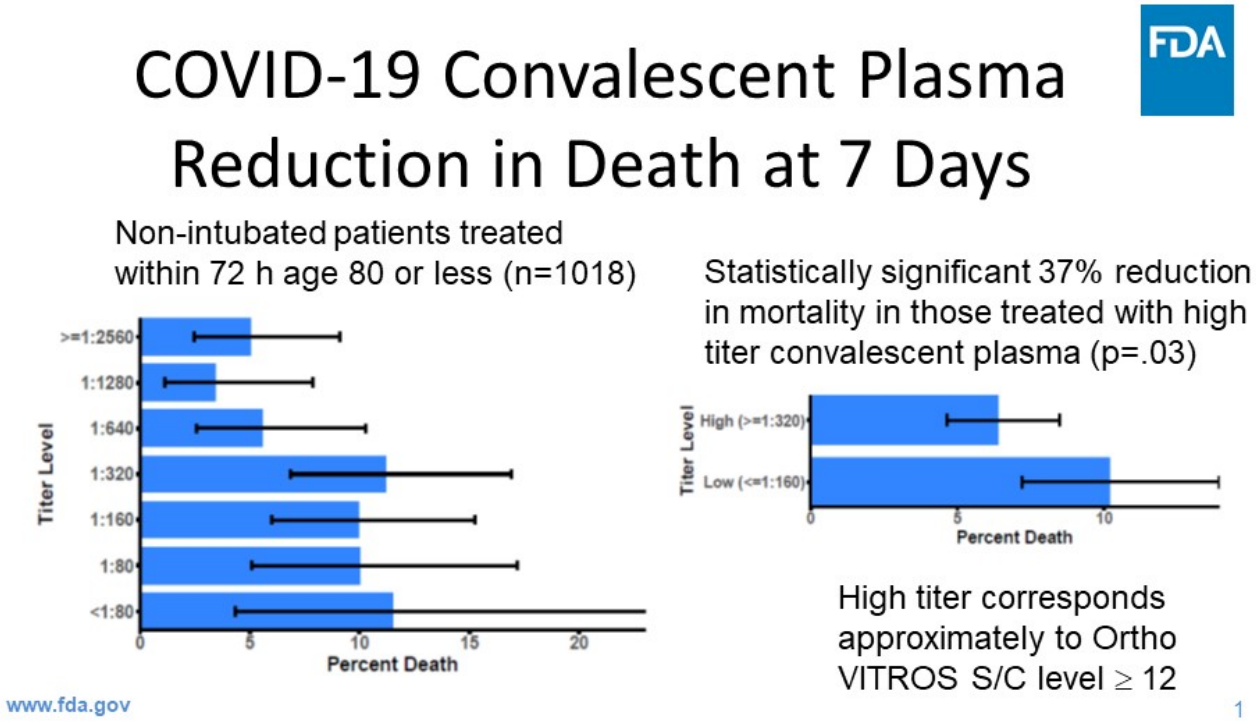
Scientific Evidence on Convalescent Plasma

Based on an evaluation of the EUA criteria and the totality of the available scientific evidence, the FDA's Center for Biologics Evaluation and Research determined that the statutory criteria for issuing an EUA criteria were met.

The FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that that there are no adequate, approved, and available alternative treatments.

The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of patients into any of the ongoing randomized clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet represent a new standard of care based on the current available evidence.

The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.



The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products

117. FDA: Updated Evidence to Support the Emergency Use of COVID-19 Convalescent Plasma – as of 9/23/2020. https://www.fda.gov/media/142386/download

Table 1. 7- and 28-Day Deaths in Patients Treated with COVID-19 Convalescent Plasma

	7-day			28-day		
	Overall (N=4330)	Not Intub (N=2488)	Not intub, ≤80 y, ≤72 h (N=932)	Overall (N=2817)	Not Intub (N=1238)	Not intub, ≤80 y, ≤72 h (N=485)
Deaths Lower Titer	14.97%	13.99%	11.29%	49.57%	49.43%	46.63%
Deaths Higher Titer	13.61%	11.00%	6.27%	46.21%	41.48%	33.23%
Absolute Improvement	1.36%	2.99%	5.02%	3.36%	7.95%	13.40%
Relative Improvement	9%	21%	44%	7%	16%	29%
Statistical Significance	Not significant	Significant p=0.03	Significant p=0.008	Not significant	Significant p=0.004	Significant p=0.004

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129. 2021-03-02 NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms – Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms

The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was: https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1
There are no reported results on the ClinicalTrials website of which the NIH is making its decision to halt the trial. The trial was underpowered where there was no stratification by age and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: **SIREN**, **S**trategies to **I**nnovate eme**R**g**EN**cy Care Clinical Trials, https://clic-ctsa.org/node/9426 .

NIH Announcement to discontinue the trial on March 2, 2021:

Launched in August 2020, the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO(link is external)) was being conducted at 47 hospital emergency departments across the United States and had enrolled 511 of the 900 participant recruitment goal. It was specifically looking at the effectiveness of COVID-19 convalescent plasma – blood plasma derived from patients who have recovered from COVID-19 – in adults who came to an emergency department with mild to moderate symptoms they had for a week or less. These patients also had at least one risk factor associated with severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease, but none were ill enough at the time to be hospitalized.

(C3PO(link is external) https://siren.network/clinical-trials/c3po

C3PO Clinical Trial of COVID-19 Convalescent Plasma of Outpatients

Registered with ClinicalTrials.gov: NCT04355767
{
https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1
This is a registered NIH ClinicalTrials.gov
Award Number: 1OT2HL156812-01
Status: No new randomizations as of February 25, 2021.
NIH Press Release (March 2, 2021)

- Media inquiries: Refer to **Lenora Johnson, DrPH, MPH** and **Mark Sampson**, and to this press release.

The Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) is a multi-center randomized, single blind, two arm, placebo controlled phase III trial with blinded outcome assessment to establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.

COVID-19 is a respiratory illness caused by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). As of May 1, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. The majority (80%) of cases are categorized as mild, while approximately 15-20% of cases are categorized as severe, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure. Among the 5% who develop severe disease, as many as 50% die. At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease.

Passive antibody therapy using plasma from donors who have been infected and then recovered (convalescent plasma, CP) contains neutralizing antibodies against the infectious agent. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic. Use of CP for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. At this moment, there is no high quality evidence to support the efficacy of CP for treating COVID-19 illness. Conceptually, CP has the highest chance of showing efficacy if used for early treatment of patients at the highest risk for severe disease and mortality.

The overarching goal of this trial is to confirm or refute the role of passive immunization as a safe and efficacious therapy in preventing the progression from mild to severe/critical COVID-19 illness and to understand the immunologic kinetics of anti-SARS-CoV-2 antibodies after passive immunization.

For more information on C3PO and convalescent plasma go to our In the News page. (https://siren.network/clinical-trials/c3po/in-the-news)

C3PO IN THE NEWS

March 10, 2021

- Convalescent Plasma Strikes Out As COVID-19 Treatment
  https://www.npr.org/975365309

October 22, 2020

- OHSU reserchers say they're having trouble recruiting patients for COVID-19 convalescent plasma trial
  https://www.kptv.com/ohsu-researchers-say-theyre-having-trouble-recruiting-patients-for-covid-19-convalescent-plasma-trial/video_767f3558-10aa-5201-ad47-94322b60070d.html?block_id=988363

September 8, 2020

- NIH clinical trial explores use of convalescent plasma in at-risk outpatients with early COVID-19
  https://www.nhlbi.nih.gov/news/2020/nih-clinical-trial-explores-use-convalescent-plasma-risk-outpatients-early-covid-19

August 25, 2020

- UF Health enrolls first patients in national COVID-19 study on convalescent blood plasma

  https://m.ufhealth.org/news/2020/uf-health-enrolls-first-patients-national-covid-19-study-convalescent-blood-plasma

August 19, 2020

- New clinical trial at OHSU tests donated antibodies

  https://news.ohsu.edu/2020/08/18/new-clinical-trial-at-ohsu-tests-donated-antibodies

August 6, 2020

- Will COVID-19 finally provide an answer on convalescent plasma?

  https://www.medpagetoday.com/infectiousdisease/covid19/87936

August 3, 2020

- UM and Other Michigan hospitals to treat COVID-19 patients with convalescent plasm.

  https://www.michiganradio.org/post/um-and-other-michigan-hospitals-treat-covid-19-patients-convalescent-plasma

July 30, 2020

- Michigan hospitals test if plasma from recovering patients can curb COVID-19

  https://www.bridgemi.com/michigan-health-watch/michigan-hospitals-test-if-plasma-recovering-patients-can-curb-covid-19

- Researchers at the University of Michigan's Michigan Medicine and three other medical centers were awarded a total of $7 million from the National Heart, Lung, and Blood Institute (NHBLI) to study convalescent plasma in reducing symptoms of COVID-19 in patients with mild cases, Michigan Medicine announced Thursday.

  https://www.clickondetroit.com/video/health/2020/07/30/michigan-medicine-7-million-in-funding-for-covid-19-therapy-trial/

- Michigan Medicine and three other medical centers receive $7 million COVID-19 outpatient convalescent plasma therapy trial

  https://www.uofmhealth.org/news/archive/202007/michigan-medicine-and-three-other-medical-centers-receive-7?fbclid=IwAR2Rr1QbiOj6OxC0dcbv2Hw0Cn6uMlnx0BTz-buGJCf4SozAqutNDa6_1qo

- Trump urges people who who have recovered from COVID-19 to donate blood plasma

  https://www.washingtonpost.com/health/2020/07/30/trump-urges-people-who-have-recovered-covid-19-donate-plasma/

  https://www.c-span.org/video/?474383-1/president-trump-roundtable-discussion-donating-plasma

July 29, 2020

- UPMC studying whether convalescent plasma help coronavirus patients with mild symptoms

  https://pittsburgh.cbslocal.com/2020/07/29/coronavirus-study-convalescent-plasma/

- COVID-19 trial to study convalescent plasma in outpatient setting

  https://web.musc.edu/about/news-center/2020/07/29/covid19-trial-to-study-convalescent-plasma-in-outpatient-setting

March 10, 2021

- Convalescent Plasma Strikes Out As COVID-19 Treatment
  https://www.npr.org/975365309

2021-03-10 Harris R: Convalescent plasma strikes out as COVID-19 Treatment. NPR, March 10, 2021, 5:01 AM ET

More than half a million Americans have received an experimental treatment for COVID-19 called convalescent plasma. But a year into the pandemic, it's not clear who, if anyone, benefits from it.

That uncertainty highlights the challenges scientists have faced in their attempts to evaluate COVID-19 drugs.

On paper, treatment with convalescent plasma makes good sense. The idea is to take blood plasma from people who have recovered from COVID-19 and infuse it into patients with active infections. The antibodies in the donated plasma, in theory, would help fight the virus.

Based on that idea, last March Dr. Nicole Bouvier at the Icahn School of Medicine at Mount Sinai Hospital in New York decided to give it a try.

She recalls thinking, "we have this new disease that didn't have any known therapies, and convalescent plasma has been used in new epidemic and pandemic diseases," as recently as in an Ebola outbreak in West Africa a few years ago.

She says she was the first doctor to get special permission from the Food and Drug Administration to use it as an experimental treatment.

It was a huge commitment to line up people willing to donate plasma as well as to treat patients themselves, "so it was a big production," she says. "We ultimately screened over 70,000 people" and identified around 20,000 who had high antibody levels in their blood plasma.

Mount Sinai treated more than 1,400 patients, including throughout the height of New York City's nightmarish COVID-19 outbreak last spring. But all the while Bouvier had no idea whether the plasma really worked.

Finally, a couple of weeks ago, she had seen enough data from carefully controlled studies — and decided to stop offering the treatment.

"The straw that broke the camel's back was two very large cohort trials," she says.
The RECOVERY Trial in the United Kingdom had studied more than 10,000 volunteers and found no benefit. Another one called CONCOR-1, run by Canadians, had studied nearly 1,000 patients. It, too, stopped recruiting new patients because doing so would have been futile.

But those studies focused on people sick enough to be in the hospital. Dr. Arturo Casadevall at the Johns Hopkins Bloomberg School of Public Health is one of the prime advocates for convalescent plasma. He says he thinks the treatment needs to be done sooner, in the outpatient setting.

"From the very beginning here at Hopkins we set out to do outpatient trials," he says. "The trials were set up in March [of 2020], however it took many months to get the money to do it." With taxpayer money nowhere to be found, the study ultimately went forward with funding from the billionaire Michael Bloomberg, Casadevall says.

A year later, the study at Hopkins still doesn't have results. And it's not just a question of funding. The entire U.S. medical research system isn't set up to do what's needed to identify new treatments during a pandemic.

Dr. Derek Angus, chair of critical care medicine at the University of Pittsburgh, says that in a public health emergency scientists should be able to evaluate new treatments at hundreds of hospitals, in a matter of months.

"People might roll their eyes and say that's impossible, but that's largely what the United Kingdom has done," Angus says. "For all our capacity in the United States, it's depressing that we can't do a U.S. version."

The U.K. was able to launch its vast study quickly because Britain has a national health system that not only provides treatment but can conduct research. Research in the U.S. is balkanized among universities, drug companies and funders.

"We pride ourselves on having a very federated, independent system," Angus says. "But, gosh, that is very hard to turn on a dime to solve national problems."

To give just one example, a national network of emergency room physicians got federal funding to treat people with convalescent plasma, in a study named C3PO. Their patients were sick enough to show up in the emergency room, but well enough to go home afterward.

"We should have been able to get this done as quickly as they did in the U.K.," says Dr. Kevin Schulman at Stanford University. "It was just a much slower process to set up."

Schulman at Stanford was responsible for some of the logistics. And they were a nightmare, he says.

"I said tongue in cheek at some point when we had five patients in our study that we had at least 500 people touch a paper for the five patients we had recruited. And that's the opposite in the UK."

"Some of the contracts for the trial we are still negotiating even today," he adds. "You know, the U.K. didn't have any of that."

The C3PO study recently stopped recruiting patients. It had enrolled about 500 out of a planned 900, but an independent monitoring board concluded that continuing would have been futile. This further casts doubt on the value of convalescent plasma.

"I don't see any point in offering plasma outside a clinical trial," says Angus from Pitt.

Several trials are ongoing. And there's still a chance that some of them could identify a group of patients, treated at a particular time with a particular concentration of plasma, who would benefit. So Bouvier at Mount Sinai hasn't given up on it completely.

In retrospect, it's understandable why convalescent plasma doesn't help people hospitalized with significant illness, she says. Serious illness is caused primarily by the body's reaction. Respiratory viruses like these don't persist for long. "They're sort of like, 'wham, bam, thank you, ma'am.' And then they're gone," Bouvier says.

"If a study comes along that identifies a population in whom convalescent plasma is useful, we will use it in that population" she says.

And if it does appear to be helpful for people who are early in the course of disease, that raises another question: Would plasma be better than the monoclonal antibody drugs already authorized by the Food and Drug Administration for that purpose and easier to use?

Casadevall at Hopkins argues that plasma might be better, especially if new virus variants can evade the antibody drugs. Antibodies in the plasma of people who have recovered have apparently been successful in controlling whatever virus they encountered, so the treatment actually evolves along with the pandemic.

But to figure out whether convalescent plasma is better than monoclonal antibodies could require another large, time-consuming study in a research system not set up to be nimble.

You can contact NPR Science correspondent Richard Harris at rharris@npr.org.

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https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

What follows is what I wrote two years regarding this study and it is just as relevant today as it was then. Much of my analyses and discussions in the spiral bound book (references 12-14 +), references 7,9,10, and my correspondence with the NIAID, FDA, and The White House are linked to Korley, et. al.: Early convalescent plasma for high-risk outpatients with COVID-19, N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] and its Supplement.

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

> The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include **NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O.** In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and **NOT** by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960. https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the Supplementary Appendix which is very important can be found at (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf).

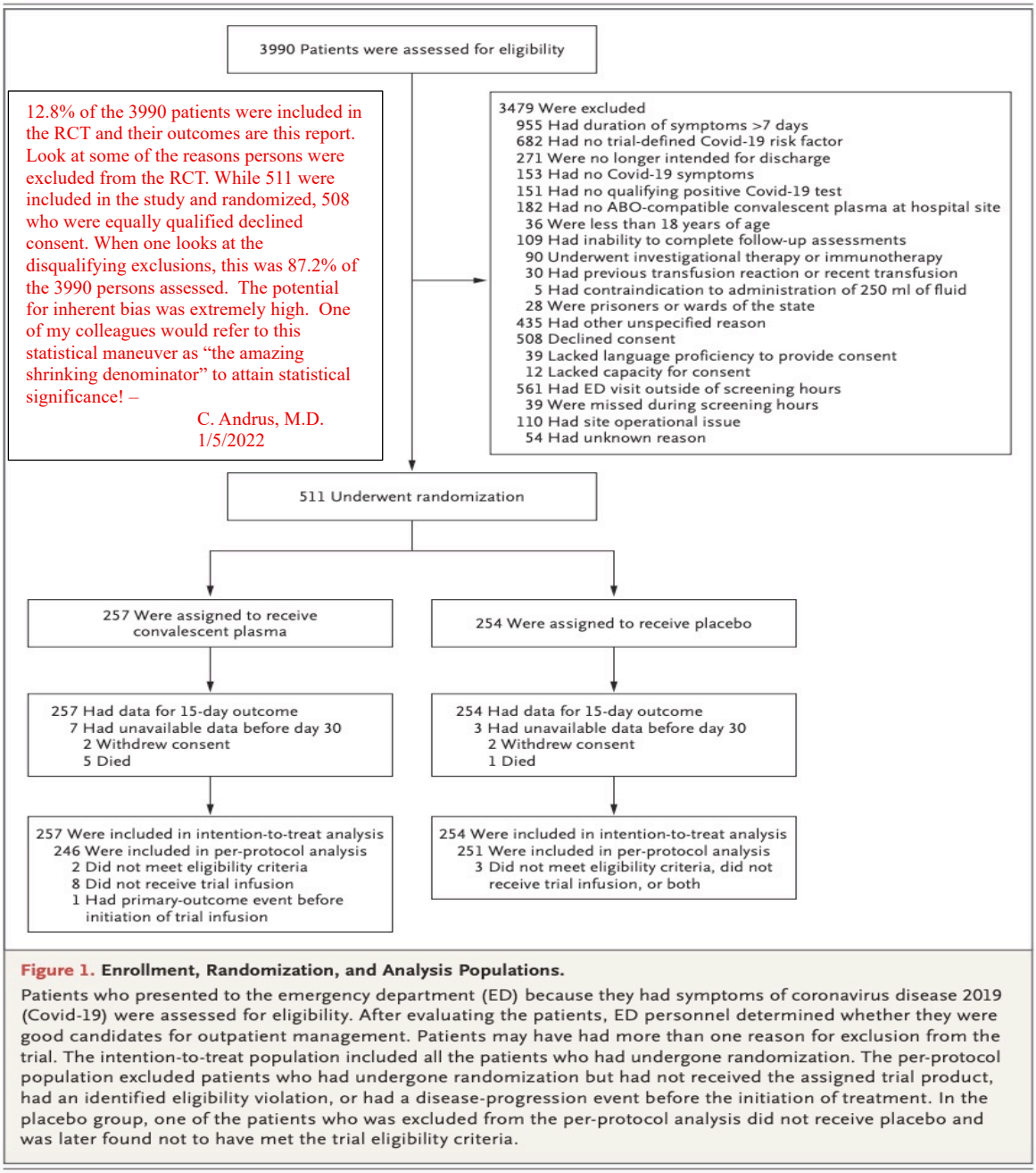
3990 Patients were assessed for eligibility
12.8% of the 3990 patients were included in the RCT and their outcomes are this report. Look at some of the reasons persons were excluded from the RCT. While 511 were included in the study and randomized, 508 who were equally qualified declined consent. When one looks at the disqualifying exclusions, this was 87.2% of the 3990 persons assessed. The potential for inherent bias was extremely high. One of my colleagues would refer to this statistical maneuver as "the amazing shrinking denominator" to attain statistical significance! –
C. Andrus, M.D.
1/5/2022
3479 Were excluded
955 Had duration of symptoms >7 days
682 Had no trial-defined Covid-19 risk factor
271 Were no longer intended for discharge
153 Had no Covid-19 symptoms
151 Had no qualifying positive Covid-19 test
182 Had no ABO-compatible convalescent plasma at hospital site
36 Were less than 18 years of age
109 Had inability to complete follow-up assessments
90 Underwent investigational therapy or immunotherapy
30 Had previous transfusion reaction or recent transfusion
5 Had contraindication to administration of 250 ml of fluid
28 Were prisoners or wards of the state
435 Had other unspecified reason
508 Declined consent
39 Lacked language proficiency to provide consent
12 Lacked capacity for consent
561 Had ED visit outside of screening hours
39 Were missed during screening hours
110 Had site operational issue
54 Had unknown reason
511 Underwent randomization
257 Were assigned to receive convalescent plasma
254 Were assigned to receive placebo
257 Had data for 15-day outcome
7 Had unavailable data before day 30
2 Withdrew consent
5 Died
254 Had data for 15-day outcome
3 Had unavailable data before day 30
2 Withdrew consent
1 Died
257 Were included in intention-to-treat analysis
246 Were included in per-protocol analysis
2 Did not meet eligibility criteria
8 Did not receive trial infusion
1 Had primary-outcome event before initiation of trial infusion
254 Were included in intention-to-treat analysis
251 Were included in per-protocol analysis
3 Did not meet eligibility criteria, did not receive trial infusion, or both

Figure 1. Enrollment, Randomization, and Analysis Populations.

Patients who presented to the emergency department (ED) because they had symptoms of coronavirus disease 2019 (Covid-19) were assessed for eligibility. After evaluating the patients, ED personnel determined whether they were good candidates for outpatient management. Patients may have had more than one reason for exclusion from the trial. The intention-to-treat population included all the patients who had undergone randomization. The per-protocol population excluded patients who had undergone randomization but had not received the assigned trial product, had an identified eligibility violation, or had a disease-progression event before the initiation of treatment. In the placebo group, one of the patients who was excluded from the per-protocol analysis did not receive placebo and was later found not to have met the trial eligibility criteria.

In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum ß that the researchers agreed upon for a valid study), it proceeded to conclude that early

administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: …for the SIREN-C3PO Investigators* where the "*" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

> Has at least one study defined risk factor for severe COVID-19 illness:
>
> Age ≥ 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. **Characteristics of the Patients at Baseline**:

Characteristic	**Convalescent Plasma (N=257)**	**Placebo (N=254)**
Median age (IQR)	54 (42-62)	54 (40-62)

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participattion in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes?

131. Siegel JP, Director, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA), Department of Health and Human Services: Biologics License No. 1252, (Reference No.: 97-1359)—Under this license you *(MedImmune, Inc.)* are authorized to manufacture the product Palivizumab. Palivizumab is to be used for prophylaxis for serious lower respiratory tract disease, caused by respiratory syncytial virus, in pediatric patients at high risk of RSV disease. Public Health Service, Food and Drug Administration, June

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150 Emerald Green Ct.
St. Louis, MO. 63141
candrus600@aol.com
Home phone: 314-455-9482
Wife's cell: 314-809-9634

NIH NIAID Case #12276

February 14, 2025

Jeanne Marrazzo, M.D., M.P.H.
Director, National Institute of Allergy and Infectious Diseases
(DHHS/NIH/NIAID/OD)
5601 Fishers Lane
Rockville, MD 20892
NIAID switchboard (301) 402-2126
Jeanne.marrazzo@nih.hhs.gov

Dear Dr. Marrazzo:

As the Director of the National Institute of Allergy and Infectious Diseases (NIAID), you are the boss (accountable administrator--previously directed by Dr. Anthony Fauci, M.D.)[1] of the Institute that has been central in acquiescing to and the abrogation of a comprehensive, incorrect interpretation of Medical history: An on-going revision of clinical immunology by ignoring the significance of the **use of exogenous immunoglobulins (*Passive Immunization)* in the treatment of a novel virus within 72 hours of diagnosis for all**.[2-15] In short, all MD's and DO's of the NIAID that each personally swore *Primum non Nocere*[16] when they graduated from medical school, have failed to live up to their individual promises to--*do no harm*-by acquiescing/condoning confusion and dismissal of foundational teachings by promoting vaccination only (*Active Immunization*) with a minimization, *de facto* abandonment of individual infected patients, of that which they were taught in their basic science years of medical school regarding early treatment (within <72 hours of diagnosis) to all individuals infected with viruses with *Passive Immunization* and antivirals.[2-7,10,12-15] In clinical medicine, the differences between *Active* and *Passive Immunization* are distinct, well-grounded, and their unique applications are fundamental. Restricting application of therapeutics to select qualitative groups of patients by risk assessment, (e.g.: old age, diabetes, hypertension, obesity), etc. instead of treatment (not prophylaxis) to all is consistent with patient abandonment by subliminal rationing which is unethical.

Shame on the physicians of the NIAID! Shame on the NIH for having relegated to historical obscurity the URL: https://www.covid19treatmentguidelines.nih.gov [17] to a server farm on August 17, 2024, so that all 72 iterations[18] of the NIH COVID-19 Treatment Guidelines cannot be easily discoverable unless the aforementioned URL is entered into the *Wayback Machine* of the *Internet Archive* yielding:
https://web.archive.org/web/20250000000000*/https://www.covid19treatmentguidelines.nih.gov/
One can find 4,983 saved captures of the 72 iterations between April 21, 2020 and August 17,

2024. This is legally a gross violation of the Sarbanes-Oxley Act of 2002, 18 U.S.C. §151(c)(1)[20-22] and destroys the organized documentation for history of how the NIH, the NIAID, the FDA, the CDC, the PHS, U.S. Medicine and U.S. Medical Academia, and the World responded to the COVID-19 pandemic—resultant from individuals infected with coronavirus, SARS-CoV-2, throughout the World.

Attached with this letter is the collection of articles within the accompanying spiral-bound book including a cover letter to President Joseph Biden that I submitted in my final correspondence to the Biden White House on January 18, 2025, via USPS (tracking number: 9405 5036 9930 0739 9678 26) as a continuation of my submissions to the NIAID, the FDA, the VA, and *The White House* over the last five years under the designation of **NIH NIAID Case #12276** and specifically my response to President Biden's letter to me of July 17, 2023.[7,10,12-15] (As this spiral-bound book was officially submitted to President Biden before the end of his term-in-office, it should be preserved in President Biden's presidential papers by the U.S. National Archives: The Presidential Records Act [PRA; 44 U.S.C. §§2201-2209][23-25]). The table of contents[12-14, etc.] of the spiral bound document sent to you today is:

0 Cover letter to President Biden regarding:
0.1 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals
0.2 Attachment I Euphemistical Obfuscation in Clinical Medicine
0.3 Attachment II Submissions to the Internet Archive
0.4 Attachment III Reductio ad Absurdum
0.5 Attachment VI Validation letter from the NIH NIAID establishing NIAID Case #12276
0.6 Attachment V 1977 NEJM letter of Case of Chronic Denial with Alfred Gilman response
0.7 Attachment VI Tables re Sources Definitions and Statistics
0.8 Attachment VII Letters to Members of Congress and Pres Trump 8_23_2020 and 8_28_2020
0.9 Attachment VIII) 08 076.0 2021-09-19 Tragedy of Electronic Overwriting
1.0 REFERENCES of ATTACHMENTS I – VIII
2.1 Table 1- Digital vs. Analog—Yes, No, Maybe in Medicine and Treatment of Covid-19
2.2 Definitions_Fundamentals_Legal_Mandates background
2.3 2024-11-23 Tables 2-6
2.4 References for Tables 1 – 6
3 2024-11-23 Some Pertinent Transcripts and Excerpts

In June 2020, Dr. Fauci directed Kara M. Harris, MPH, Communications Officer for the NIAID, to acknowledge for him to me on June 10, 2020, my correspondence of June 2020 to Dr. Fauci--0.5 Attachment VI Validation letter from the NIH NIAID establishing NIAID Case #12276, June 10, 2020. That was the first and last time I received any written correspondence from the NIAID for the next ~five years. So, I just kept submitting to the NIH NIAID, *et. al.*, under case file #12276 so as to preserve for history officially and legally this information. Much of my correspondence has been posted in six uploads to the *Internet Archive* over the last few years.[7-11]

While Dr. Fauci has retired from the NIH NIAID[1] and was pardoned by President Biden[26], he is thus no longer responsible for the ongoing activities of the NIH NIAID—you are.[27] As you will read in 0.1 - 0.4 and 0.6 and 0.9, the pervasiveness of the processes of electronic overwriting, URL destruction, *de facto* rationing of treatment only by arbitrarily limiting administrations to only "at risk" individuals and thus abandoning <u>all</u> acutely infected individuals has promoted ignorant duplicity and chronic denial (0.6 of the table of contents)--which is reprehensible yet inundates the television media pervasively today. As the Director of the NIAID[27], you are one of

the responsible oversight individuals for this ongoing unethical inappropriateness. Over a million people died from COVID-19 in the U.S.A. over roughly the first year in 2020 in which the vast majority of acutely infected individuals were not treated or incorrectly treated late (>72 hours from diagnosis and only when in the end-stages of the disease) with exogenous antibodies (i.e. convalescent plasma or sera, monoclonal antibodies, or monoclonal antibody cocktails) and the antiviral Remdesivir (VEKLURY®).

What I find most distasteful is the fact that U.S. Medicine condoned the incorrect modification of foundational Medical history and teachings. The use of *Passive Immunization* for treatment versus prophylaxis—vaccination of the uninfected, (Active Immunization)--is over 140 years old dating back to Emil von Behring[2,28-30] and Louis Pasteur.[2,3,31,32] The FDA, the NIH, the NIAID, the CDC, the PHS, etc. so misled / confused practicing physicians and their patients that nobody really knows how to **clinically treat** (not prophylax) an acute viral infection with immunoglobulins[33-38] like RSV [7,10,12-14,17], COVID-19[6,7,10,12-14], M-pox (moneypox)[39-42] , etc. Most have forgotten that while General Washington's victory of the Revolutionary War was aided by the vaccination of American troops against smallpox during our Revolution from England, and the mandated use of William Jenner's vaccine successfully eradicated smallpox from the U.S.A. in the mid-1940s, it took the World Health Organization (WHO) about a decade of tracking, isolation, vaccination, and synergistic treatment with *passive immunization* in those infected with or acutely exposed to smallpox to eradicate clinically smallpox from the World.[43-63]

How long will it take us to review, revise, and treat correctly COVID-19, RSV, monkeypox, (and even influenza), etc. synergistically with exogenous antibodies and antivirals within 72 hours of diagnosis in **all** acutely infected individuals by vaccination throughout the general public? Note, that the present JYNNEOS™ vaccine is for both smallpox and monkeypox (M-pox).[64] It is suggested in the literature that there is a significant portion of the present U.S.A. population born before the 1980s alive that were mandatorily vaccinated for smallpox with an attenuated Orthopoxvirus vaccine who demonstrate long-standing pox immunity thus reducing the incidence and the severity of illness when M-pox is contracted.[65-67] General vaccination against Respiratory Syncytial Virus (RSV) of **all** children consistent with that which is mandated with other viruses of the Paramyxoviridae family, i.e. measles and mumps, will decrease the vector pool in vaccinated families over time as has happened as a result of the MMR. Early treatment (<72 hours from diagnosis) of **all** acutely RSV-infected individuals with monoclonal antibodies, e.g. Palivizumab (Synagis), Nirsevimab (Beyfortus), etc. and the antiviral, ribavirin, should be treatments for all ages.[12-15,17,68-73] Today, acute COVID-19 infection in the individual regardless of vaccination status should be treated in **all** with Paxlovid[74] which *de facto* has subliminally become financially prohibitive for the infected individual without financial supplementation (~$1,400 for a five-day treatment when the average production cost for a five-day treatment is ~$13.38).[75]

What I find most dismaying is that of U.S. Medicine's collective dismissal / denial of the foundational elements temporized by bureaucratic stupidity as epitomized in Dr. Fauci's book[1] on pages 403-404 regarding President Trump in October 2020:

> His bout with COVID did not go smoothly. After he was hospitalized at Walter Reed National Military Medical Center, where U.S. presidents go for health care that might require hospitalization, the president called me and told me how impressed he was with the suite he was in. "Have you ever been

> here?" he asked. "Yes, Mr. President," I answered. "I was there in 1973 when I helped care for President Nixon, who had viral pneumonia." After commenting on my voice, which he said sounded much better following surgical removal of my vocal cord polyp, the president described his treatment, which included the Regeneron monoclonal antibody. A monoclonal antibody is an artificially produced antibody usually administered intravenously that is highly specific for a given target, in this case a part of the spike protein of SARS-CoV-2. Early clinical studies suggested that it might be an effective treatment for COVID. President Trump told me what was already being reported in the media—that he was very sick when he came into the hospital and "felt like fucking shit." But a few hours after receiving the Regeneron monoclonal antibody, he felt better than he had in years. Bottom line: he wanted me to get Regeneron monoclonal antibody emergency use approval.
>
> I explained that the monoclonal antibody therapy was still in clinical trials. He said the most important clinical trial had been done—that is, on him, the president—which was all we needed to know. He wanted me to get back to him, and get the treatment out to millions of sick people.
>
> "Mr. President," I told him. "This is an FDA regulatory issue, and so there is nothing I can do about it." He then said the FDA would listen to me. I did not want to argue with him, but I thought to myself that he did not seem to appreciate the complex process of drug approval. It was a friendly but strange conversation.

Indeed, as was emphasized by Dr. Fauci's *New England Journal of Medicine* (NEJM) landmark review article of 2018: Marston HD, Paules CI, Fauci AS: Monoclonal Antibodies for Emerging Infectious Diseases—Borrowing from History (https://www.nejm.org/doi/full/10.1056/NEJMp1802256) and his accompanying interview https://www.nejm.org/do/10.1056/NEJMdo002465/full/, exogenous antibodies (polyclonal, e.g. convalescent plasma and serum and monoclonal antibodies / cocktails) are the mainstay of treating within 72 hours of diagnosis acutely-infected individuals synergistically with antivirals.[17] If Dr. Fauci had impressed this on the NIAID and the FDA over the last quarter-of-a-century, Palivizumab (Synagis) could have been administered within 72 hours of diagnosis to all adults contracting RSV diminishing approximately 350,000 adult deaths extrapolated from CDC data.[76] Shame on the NIAID, the FDA, etc. as Palivizumab and Nirsevimab continue to be restricted/limited/rationed to children with concomitant high risk conditions only instead of immediate provision for the entire acutely infected population within 72 hours of diagnosis. Such withholding and therapeutic restrictions are unethical--tantamount to the Tuskegee Syphilis Project of the mid-20th century[77-78] – but, at a national level. As Dr. Fauci has retired and was pardoned by President Biden[26], the FDA and the NIAID—of which you are the present "boss"[27]—are responsible and accountable to address this ongoing unethical process of treatment abandonment of the vast majority of the American populous before the American people—not for just RSV but also for COVID-19, influenza, etc. that could be treated early and systematically with convalescent plasma / monoclonal antibodies / immunoglobulins in synergism with antivirals!

While Dr. Fauci stated[1] that for approximately 40 years he was a named editor of *Harrison's Principles of Internal Medicine* (editions 11-21, being Editor-in-Chief of editions 14,17)[79], this major textbook fails miserably in the provision of a foundational, all-encompassing algorithm in the TREATMENT within 72 hours of diagnosis (not prophylaxis) of all acutely infected individuals with exogenous antibodies and antivirals directed towards the specific virus. Vaccination (Active Immunization) is ***NOT*** a treatment of acutely infected individuals at all but prophylaxis—only effective when the patient is not infected and somehow otherwise not immunosuppressed! The NIH, FDA, and *The New England Journal of Medicine* should be ashamed of collectively condoning, acting upon, and publishing the SIREN-C3PO study

(NCT04355767)[80] which is a statistically spurious, underpowered research project—funded by the NIH, acted upon by the FDA, and published by *The New England Journal of Medicine*.[81] Please read in the attached spiral-bound book (especially 0.1, 0.2, and 0.4) and references 7, 9-14 which contain well-documented analyses of the inappropriateness that led to the subsequent >1 million deaths from COVID-19 during the first year of the American COVID-19 epidemic from March 2, 2020 onward. On March 2, 2020, Dr. Fauci was physically present and witnessed silently in *The White House* cabinet room when Dr. Leonard Schleifer, M.D., Ph.D. incorrectly explained and fused the two distinctly immunologically different processes of *Active Immunization* (prophylaxis) and *Passive Immunization* (treatment) into "Passive vaccination."[82]

Dr. Fauci, in self-preservation, stated in his book[1] on page 400:

> We were a subdued group as we left, but I felt a sense of relief that I had told it like it was. Now whatever happened would happen. But I was not worried that Donald Trump would fire me. First, I did not believe that he was really angry with me, and I also had the sense that he respected people who were not afraid to stand up to him. Next, though I suspect he did not actually know this, since I was a civil servant, he could remove me from the White House, but I could not be fired as NIAID director without proving serious cause, a whole separate procedure over which he had no control.

Although Dr. Fauci's statement regarding the Civil Service Retirement System is legally true and Federal employees should not be subjected to firing without cause, President Trump in the past weeks has seemingly denied due process for all Executive Branch employees and President Trump (and Elon Musk) and advocate for firing without cause.[83]

One of the most disappointing exchanges I witnessed in the last five years was Dr. Fauci's interview[84] by Margaret Brennan on *Face the Nation* that aired on November 28, 2021:

> MARGARET BRENNAN: But just to button that up. Why aren't we having a national conversation about what went wrong? I mean, apart from this room right now, why isn't there a 9/11 type commission?

> DR. FAUCI: Yeah, I think what's going to happen is that you are going to see that for sure, MARGARET. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through with already 760,000 Americans dying and 40 plus million at least being infected, close to six million people globally dying. And we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out. So people should not think that that's not going to happen. It's not happening now because everybody's focusing on getting this thing under control.

Well, no such "autopsy" has ever occurred. What should have occurred throughout the American COVID-19 epidemic were weekly M&M conferences[85-86] in which overall clinical treatments—successes and failures--for the infected individual patients were discussed. This probably demonstrates my naivete, but I will be happy to present myself in person--maybe in the Secretary's conference room on the 10th floor of VA Central Office (across Lafayette Square from *The White House*) in an official M&M conference format as this is a legally protected venue from discovery.[87-88] You could bring a few fellow physicians that you feel would be appropriate who were and are intimately involved in the NIAID process, and I can ask a few surgeons I know who might willingly be in attendance who still believe in the M&M process—like myself, they are not research immunologists nor infectious disease specialists, but they are

practicing clinicians who care for individual patients daily and they believe in a weekly M&M conference to review critically their short-comings and mistakes in such a venue.

Dr. Marrazzo, after you have time to look over the attached spiral-bound book that I am mailing to you with this cover letter, (USPS 9405 5036 9930 0744 9254 84), give me a call—my home phone number is 314-455-9482 and my wife, Pam's cell is 314-809-9634. If you should pass through St. Louis, you (and anyone who you might think appropriate, e.g.: Drs. Fauci, Collins, Marks (FDA), Birx, Joyner, the Editors of the NEJM and/or the JAMA, etc.) are always welcome in our home. As a former physician and surgeon[89] of the Veterans Health Administration, U.S. Department of Veterans Affairs, I see this submission as my duty to the United States of America to continue my interaction with the NIH NIAID under case #12276. I will submit duplicates of this cover letter, my draft book submitted to President Biden on January 18, 2025, and an SDHC disc to the appropriate U.S. Offices of the Inspectors General, etc. regarding the past and ongoing historically aberrant, erroneous activities pointed out by these submissions.

As I stated at the end of my paper[90] of 23 years ago: "To Err Is Human": Uniformly reporting medical errors and near misses--A naïve, costly, and misdirected goal, I conclude this cover letter to you, Dr. Marrazzo, with that which we, as physicians, all must strive for throughout life which was emphasized a century ago by Francis W. Peabody, M.D. before the students of the Harvard Medical School:

"…the secret of the care of the patient is in caring for the patient."

Thank you for reviewing and considering this submission.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

P.S. Today, we live in an era of Machiavellianism and Medical nihilism. The boundaries have blurred between appropriate, available treatment of the individual person acutely infected with a virus (*Passive Immunization*) versus prophylaxis-only so as to anticipate viral contraction in the future (*Active Immunization*). We have discarded key elements of Medical history. I have included with the draft submission (spiral-bound book) to President Biden on January 18, 2025, several books and articles that chronical the history of *Passive* and *Active Immunization*. (I have left out *Harrison's Principles of Internal Medicine*, *Plotkin's Vaccines,* and Fauci's *On Call—A Doctor's Journey in Public Service* as there are probably multiple copies around the NIAID or can be found easily on-line.) That which are included with this submission in my mailing to you today are all under **NIH NIAID case #12276 and therefore should be preserved for history by the NIAID**:

1. Huff D, (pictures by Irving Geis): *How to Lie with Statistics*. New York: W.W. Norton & Company, Inc. 1954. Online in part at:

https://online225.psych.wisc.edu/wp-content/uploads/225-Master/225-UnitPages/Unit-07/Huff_StatisticsBook_1954.pdf **{reference 91 of this cover letter}**

2. de Kruif P: *Microbe Hunters*. New York: Harcourt, Brace, and Co., 1926. (New York: Paul de Kruif, Harcourt, Brace, Co., copyright renewed 1954). https://laurieximenez.files.wordpress.com/2016/03/2-microbe-hunters-paul-de-kruif.pdf **{reference 4 of this cover letter}**

3. Haas D, Pellicer JL (illustrator): *Men of Science*, A Badger Book. Racine, Wisconsin: Whitman Publishing Company, 1959. Pgs 9-17, 73-79. https://www.amazon.com/Badger-Book-Men-Science/dp/B000GBQ9ZI **{reference 5 of this cover letter}**

4. Jacobson JM: *Immunotherapy for Infectious Diseases*. Totowa, New Jersey: Humana Press, 2002. Pages 63-97. **{reference 3 of this cover letter}**

5. Slifka MK, Amanna IJ: Passive immunization. Plotkin's Vaccines 2018: 84-95. (Especially Figure 8.2. Efficacy of passive immunity decreases with disease progression, page 88 [e6 of e23]. Copy included with this cover letter. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151993/pdf/main.pdf **{reference 2 of this cover letter}**

6. Marston HD, Paules CI, Fauci AS: Monoclonal antibodies for emerging infectious diseases – Borrowing from history. N Engl J Med 2018 April 19; 378 (16): 1469-1472. https://www.nejm.org/doi/full/10.1056/NEJMp1802256) and Dr. Fauci's commentary / interview can be found at https://www.nejm.org/do/10.1056/NEJMdo002465/full/. **{references 17 (article and on the *Internet,* Dr. Fauci's interview) of this cover letter}**

7. Otsubo R, Yasui Teruhito: Monoclonal antibody therapeutics for infectious diseases: Beyond normal human immunoglobulin. Pharmacology & Therapeutics 2022; 240: 108233, pages 1-13. **{reference 6 of this cover letter}**

The following two references regardig the ethics of Public Service in the U.S.A. that might be helpful in your internal discussions regarding this cover letter especially in the times we are now in:

1. Andrus CH, Villasenor EG, Kettelle JB, Roth R, Sweeney AM, Matolo NM: "To Err is Human": Uniformly reporting medical errors and near misses, a naïve, costly, and misdirected goal. J Am Coll Surg 2003 June; 196 (6): 911-918. doi: 10.1016/S1072-7515(03)00236-9. PMID: 12788428. **{Reference 90 of this cover letter}** https://journals.lww.com/journalacs/citation/2003/06000/_to_err_is_human___uniformly_reporting_medical.11.aspx [In January 2004, in response to the unsolicited request of Ms. Goldstein, librarian of the Joseph and Rose Kennedy Bioethics Library (JRKBL), Georgetown University, which is the bioethics repository library of the U.S. National

Library of Medicine (NLM), I submitted an original official reprint of this article of the Journal of the American College of Surgeons for inclusion in the official published files of the JRKBL. (Please note that if you try to GOOGLE this article today, it cannot be found and thus does not exist on the *Internet*. Using the URL above and then under American College of Surgeons Member login or possibly through OVID of your institution, one can access a copy of this eight-page article. The inability to access directly this article is an example of a URL lost from the *Internet*). One can locate the first page saved in 2024 in the *Internet Archive:* https://web.archive.org/web/20240422185715/https://journals.lww.com/journalacs/citation/2003/06000/_to_err_is_human___uniformly_reporting_medical.11.aspx (I will attach the Perplexity (an AI) analysis of this article with the reprint copy in this mailing.)]

2. Shulkin D, Ninth Secretary of Veterans Affairs: *It Shouldn't Be This Hard to Serve Your Country—Our Broken Government and the Plight of Veterans*. New York: **Public**Affairs, 2019. https://www.amazon.com/Shouldnt-This-Hard-Serve-Country/dp/1541762657 **{Reference 92 of this cover letter}**

References:

1. Fauci A: *On Call—A Doctor's Journey in Public Service*. USA: VIKING, Penguin Random House, LLC, 2024.

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12. Andrus CH: Generalized dismissal of early treatment with *Passive Immunization* and Antivirals (Not Prophylaxis/*Active Immunization*) in persons infected with COVID-19. Draft of entire book of January 18, 2025, mailed to *The White House* for President Joseph Biden, USPS, on January 18, 2025, and included on SDHC disc with this submission: 0.1 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals. **NIAID Case 12276.**

13. Andrus CH: **America's Fight Against Coronavirus, SARS-CoV-2, COVID-19** with mRNA vaccine prophylaxis (monoclonal *Active Immunization*) alone without implementation FOR ALL infected with COVID-19 with **synergistic, early (<96 hours from diagnosis) with exogenous immunoglobulins (*Passive Immunization*) and antivirals *OR* Euphemistical Obfuscation in Clinical Medicine, *Jesuitical* Lies by Omission and Paltering, Subliminal Bait-and-Switch, and Machiavellianism Resulting in 1,000,000+ Deaths and America's Defeat by the Non-sentient Coronavirus, SARS-CoV-2, COVID-19**. Draft of entire book of January 18, 2025, mailed to *The White House* for President Joseph Biden, USPS, on January 18, 2025, and included on SDHC disc with this submission: 0.2 Attachment I Euphemistical Obfuscation in Clinical Medicine. **NIAID Case #12276.**

14. Andrus CH: ***Reductio ad Absurdum*: The COVID-19 Tale of Two Presidents, the Ramifications of Fifty Years of American Scandal, Therapeutic Nihilism, and Medical Stupidity:**

Euphemisms[239]**:** Experimental / Investigational / EUA,
Expanded Access / Compassionate Care
FDA Authorization vs FDA Approval,
Treatment vs Prophylaxis,

Active Immunization vs Passive Immunization, etc.,

FDA Archiving reliance on non-governmental sites

FDA archived web material is maintained within the Pagefreezer platform.

and loss of information by ***electronic overwriting*** and ***destruction*** of URLs,

FDA and NIH blatant, total disregard of the Right to Try Act (PL-115-176) by never declaring a completed Phase 1(Safety) [vs Phase 2/3 Efficacy]
Clinical Trial and thus dismissing and *de facto* legally violating PL-115-176

Statistical Misdirection,

Predatory Marketing, and

> 1.1 million Americans dead associated with **withholding early** (**within 72-120 hours** of diagnosis) synergistic treatment with **Exogenous Immunoglobulins (Passive Immunization)** and **Antivirals**

Contingent on: Ignorance, Sins of Ommission, Conflicts-of-Interest, Greed

"Reform must come from within, not from without.
You cannot legislate for Virtue" James Cardinal Gibbons, "Prince of Democracy"

Face page of ***Reductio ad Absurdum*** with references only, pages 1-29. Complete section can be found in pages e30 – e130 of *0.4 BOOK 4 Biden Response to the Summary of Book 1 COVID 19 And Where We Went Wrong 2nd Attemp*, publication date 2024-03-05. https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp

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> Antibodies have been used for a century for the prevention and treatment of infectious diseases (Table 1). In bacterial disease, antibodies neutralize toxins, facilitate opsonization, and, with complement, promote bacteriolysis; in viral disease, antibodies block viral entry into uninfected cells, promote antibody-directed cell-mediated cytotoxicity by natural killer cells, and neutralize virus alone or with the participation of complement.
>
> Prior to the use of antibiotics, antibodies were the only specific agents for the treatment of certain infections. Although this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1). Since several excellent reviews are available, this article will emphasize new developments (30, 31, 101, 164, 165).
>
> Antibodies can be administered as human or animal plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or convalescing donors, and as monoclonal antibodies (Mab) (30, 164,178). The

therapeutic use of Mab is increasing dramatically, but only one (palivizumab for respiratory syncytial virus [RSV]) has been licensed for prophylaxis of an infectious disease.

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    a. But immunization in the 1770s was not what it's like today with a single injection and a low risk of mild symptoms. Edward Jenner didn't even develop his revolutionary cowpox-based vaccine for smallpox until 1796. The best inoculation technique at Washington's disposal during the Revolutionary War was a nasty and sometimes fatal method called "variolation."

b. “An inoculation doctor would cut an incision in the flesh of the person being inoculated and implant a thread laced with live pustular matter into the wound,” explains Fenn. “The hope and intent was for the person to come down with smallpox. When smallpox was conveyed in that fashion, it was usually a milder case than it was when it was contracted in the natural way.”

c. Variolization still had a case fatality rate of 5 to 10 percent. And even if all went well, inoculated patients still needed a month to recover. The procedure was not only risky for the individual patient, but for the surrounding population. An inoculee with a mild case might feel well enough to walk around town, infecting countless others with potentially more serious infections.

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> The world will be fighting coronavirus for the next three to four years as virus hot spots skip from nation to nation, and the pandemic's toll will linger for decades, said Dr. Larry Brilliant, a California epidemiologist who was part of a World Health Organization team in the 1970s that helped eradicate smallpox.
>
> But it's "not all doom and gloom," **with effective vaccines likely to emerge from dozens of candidates worldwide and effective treatments, including convalescent plasma and monoclonal antibodies, to help people recover more quickly**, said Brilliant, who chairs Ending Pandemics advisory board.
>
> "We will still be chasing the virus four years from now. But it won’t be like (today)," Brilliant told the USA TODAY Editorial Board on Monday afternoon. "It will be like the smallpox eradication program. The polio eradication program. Having yellow fever in some countries and not in others."

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    The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was: https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1
    There are no reported results on the ClinicalTrials website of which the NIH is making its decision to halt the trial. The trial was underpowered where there was no stratification by age and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: **SIREN**, **S**trategies to **I**nnovate eme**R**g**EN**cy Care Clinical Trials, https://clic-ctsa.org/node/9426 .

NIH Announcement to discontinue the trial on March 2, 2021:

Launched in August 2020, the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO(link is external)) was being conducted at 47 hospital emergency departments across the United States and had enrolled 511 of the 900 participant recruitment goal. It was specifically looking at the effectiveness of COVID-19 convalescent plasma – blood plasma derived from patients who have recovered from COVID-19 – in adults who came to an emergency department with mild to moderate symptoms they had for a week or less. These patients also had at least one risk factor associated with severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease, but none were ill enough at the time to be hospitalized.

(C3PO(link is external) https://siren.network/clinical-trials/c3po

C3PO Clinical Trial of COVID-19 Convalescent Plasma of Outpatients

Registered with ClinicalTrials.gov: NCT04355767

{
https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1

This is a registered NIH ClinicalTrials.gov

Award Number: 1OT2HL156812-01

Status: No new randomizations as of February 25, 2021.

NIH Press Release (March 2, 2021)

- Media inquiries: Refer to **Lenora Johnson, DrPH, MPH** and **Mark Sampson**, and to this press release.

The Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) is a multi-center randomized, single blind, two arm, placebo controlled phase III trial with blinded outcome assessment to establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.

COVID-19 is a respiratory illness caused by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). As of May 1, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. The majority (80%) of cases are categorized as mild, while approximately 15-20% of cases are categorized as severe, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure. Among the 5% who develop severe disease, as many as 50% die. At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease.

Passive antibody therapy using plasma from donors who have been infected and then recovered (convalescent plasma, CP) contains neutralizing antibodies against the infectious agent. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic. Use of CP for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. At this moment, there is no high quality evidence to support the efficacy of CP for treating COVID-19 illness. Conceptually, CP has the highest chance of showing efficacy if used for early treatment of patients at the highest risk for severe disease and mortality.

The overarching goal of this trial is to confirm or refute the role of passive immunization as a safe and efficacious therapy in preventing the progression from mild to severe/critical COVID-19 illness and to understand the immunologic kinetics of anti-SARS-CoV-2 antibodies after passive immunization.

For more information on C3PO and convalescent plasma go to our In the News page. (https://siren.network/clinical-trials/c3po/in-the-news)

C3PO IN THE NEWS

March 10, 2021

- Convalescent Plasma Strikes Out As COVID-19 Treatment
  https://www.npr.org/975365309

October 22, 2020

- OHSU reserchers say they're having trouble recruiting patients for COVID-19 convalescent plasma trial
  https://www.kptv.com/ohsu-researchers-say-theyre-having-trouble-recruiting-patients-for-covid-19-convalescent-plasma-trial/video_767f3558-10aa-5201-ad47-94322b60070d.html?block_id=988363

September 8, 2020

- NIH clinical trial explores use of convalescent plasma in at-risk outpatients with early COVID-19
  https://www.nhlbi.nih.gov/news/2020/nih-clinical-trial-explores-use-convalescent-plasma-risk-outpatients-early-covid-19

August 25, 2020

- UF Health enrolls first patients in national COVID-19 study on convalescent blood plasma
  https://m.ufhealth.org/news/2020/uf-health-enrolls-first-patients-national-covid-19-study-convalescent-blood-plasma

August 19, 2020

- New clinical trial at OHSU tests donated antibodies
  https://news.ohsu.edu/2020/08/18/new-clinical-trial-at-ohsu-tests-donated-antibodies

August 6, 2020

- Will COVID-19 finally provide an answer on convalescent plasma?
  https://www.medpagetoday.com/infectiousdisease/covid19/87936

August 3, 2020

- UM and Other Michigan hospitals to treat COVID-19 patients with convalescent plasm.
  https://www.michiganradio.org/post/um-and-other-michigan-hospitals-treat-covid-19-patients-convalescent-plasma

July 30, 2020

- Michigan hospitals test if plasma from recovering patients can curb COVID-19
  https://www.bridgemi.com/michigan-health-watch/michigan-hospitals-test-if-plasma-recovering-patients-can-curb-covid-19
- Researchers at the University of Michigan's Michigan Medicine and three other medical centers were awarded a total of $7 million from the National Heart, Lung, and Blood Institute (NHBLI) to study convalescent plasma in

reducing symptoms of COVID-19 in patients with mild cases, Michigan Medicine announced Thursday.

https://www.clickondetroit.com/video/health/2020/07/30/michigan-medicine-7-million-in-funding-for-covid-19-therapy-trial/

- Michigan Medicine and three other medical centers receive $7 million COVID-19 outpatient convalescent plasma therapy trial

  https://www.uofmhealth.org/news/archive/202007/michigan-medicine-and-three-other-medical-centers-receive-7?fbclid=IwAR2Rr1QbiOj6OxC0dcbv2Hw0Cn6uMlnx0BTz-buGJCf4SozAqutNDa6_1qo
- Trump urges people who who have recovered from COVID-19 to donate blood plasma

  https://www.washingtonpost.com/health/2020/07/30/trump-urges-people-who-have-recovered-covid-19-donate-plasma/

  https://www.c-span.org/video/?474383-1/president-trump-roundtable-discussion-donating-plasma

July 29, 2020

- UPMC studying whether convalescent plasma help coronavirus patients with mild symptoms

  https://pittsburgh.cbslocal.com/2020/07/29/coronavirus-study-convalescent-plasma/
- COVID-19 trial to study convalescent plasma in outpatient setting

  https://web.musc.edu/about/news-center/2020/07/29/covid19-trial-to-study-convalescent-plasma-in-outpatient-setting

March 10, 2021

- Convalescent Plasma Strikes Out As COVID-19 Treatment

  https://www.npr.org/975365309

2021-03-10 Harris R: Convalescent plasma strikes out as COVID-19 Treatment. NPR, March 10, 2021, 5:01 AM ET

More than half a million Americans have received an experimental treatment for COVID-19 called convalescent plasma. But a year into the pandemic, it's not clear who, if anyone, benefits from it.

That uncertainty highlights the challenges scientists have faced in their attempts to evaluate COVID-19 drugs.

On paper, treatment with convalescent plasma makes good sense. The idea is to take blood plasma from people who have recovered from COVID-19 and infuse it into patients with active infections. The antibodies in the donated plasma, in theory, would help fight the virus.

Based on that idea, last March Dr. Nicole Bouvier at the Icahn School of Medicine at Mount Sinai Hospital in New York decided to give it a try.

She recalls thinking, "we have this new disease that didn't have any known therapies, and convalescent plasma has been used in new epidemic and pandemic diseases," as recently as in an Ebola outbreak in West Africa a few years ago.

She says she was the first doctor to get special permission from the Food and Drug Administration to use it as an experimental treatment.

It was a huge commitment to line up people willing to donate plasma as well as to treat patients themselves, "so it was a big production," she says. "We ultimately screened over 70,000 people" and identified around 20,000 who had high antibody levels in their blood plasma.

Mount Sinai treated more than 1,400 patients, including throughout the height of New York City's nightmarish COVID-19 outbreak last spring. But all the while Bouvier had no idea whether the plasma really worked.

Finally, a couple of weeks ago, she had seen enough data from carefully controlled studies — and decided to stop offering the treatment.

"The straw that broke the camel's back was two very large cohort trials," she says.

The RECOVERY Trial in the United Kingdom had studied more than 10,000 volunteers and found no benefit. Another one called CONCOR-1, run by Canadians, had studied nearly 1,000 patients. It, too, stopped recruiting new patients because doing so would have been futile.

But those studies focused on people sick enough to be in the hospital. Dr. Arturo Casadevall at the Johns Hopkins Bloomberg School of Public Health is one of the prime advocates for convalescent plasma. He says he thinks the treatment needs to be done sooner, in the outpatient setting.

"From the very beginning here at Hopkins we set out to do outpatient trials," he says. "The trials were set up in March [of 2020], however it took many months to get the money to do it." With taxpayer money nowhere to be found, the study ultimately went forward with funding from the billionaire Michael Bloomberg, Casadevall says.

A year later, the study at Hopkins still doesn't have results. And it's not just a question of funding. The entire U.S. medical research system isn't set up to do what's needed to identify new treatments during a pandemic.

Dr. Derek Angus, chair of critical care medicine at the University of Pittsburgh, says that in a public health emergency scientists should be able to evaluate new treatments at hundreds of hospitals, in a matter of months.

"People might roll their eyes and say that's impossible, but that's largely what the United Kingdom has done," Angus says. "For all our capacity in the United States, it's depressing that we can't do a U.S. version."

The U.K. was able to launch its vast study quickly because Britain has a national health system that not only provides treatment but can conduct research. Research in the U.S. is balkanized among universities, drug companies and funders.

"We pride ourselves on having a very federated, independent system," Angus says. "But, gosh, that is very hard to turn on a dime to solve national problems."

To give just one example, a national network of emergency room physicians got federal funding to treat people with convalescent plasma, in a study named C3PO. Their patients were sick enough to show up in the emergency room, but well enough to go home afterward.

"We should have been able to get this done as quickly as they did in the U.K.," says Dr. Kevin Schulman at Stanford University. "It was just a much slower process to set up."

Schulman at Stanford was responsible for some of the logistics. And they were a nightmare, he says.

"I said tongue in cheek at some point when we had five patients in our study that we had at least 500 people touch a paper for the five patients we had recruited. And that's the opposite in the UK."

"Some of the contracts for the trial we are still negotiating even today," he adds. "You know, the U.K. didn't have any of that."

The C3PO study recently stopped recruiting patients. It had enrolled about 500 out of a planned 900, but an independent monitoring board concluded that continuing would have been futile.

This further casts doubt on the value of convalescent plasma.

"I don't see any point in offering plasma outside a clinical trial," says Angus from Pitt.

Several trials are ongoing. And there's still a chance that some of them could identify a group of patients, treated at a particular time with a particular concentration of plasma, who would benefit. So Bouvier at Mount Sinai hasn't given up on it completely.

In retrospect, it's understandable why convalescent plasma doesn't help people hospitalized with significant illness, she says. Serious illness is caused primarily by the body's reaction. Respiratory

viruses like these don't persist for long. "They're sort of like, 'wham, bam, thank you, ma'am.' And then they're gone," Bouvier says.

"If a study comes along that identifies a population in whom convalescent plasma is useful, we will use it in that population" she says.

And if it does appear to be helpful for people who are early in the course of disease, that raises another question: Would plasma be better than the monoclonal antibody drugs already authorized by the Food and Drug Administration for that purpose and easier to use?

Casadevall at Hopkins argues that plasma might be better, especially if new virus variants can evade the antibody drugs. Antibodies in the plasma of people who have recovered have apparently been successful in controlling whatever virus they encountered, so the treatment actually evolves along with the pandemic.

But to figure out whether convalescent plasma is better than monoclonal antibodies could require another large, time-consuming study in a research system not set up to be nimble.

You can contact NPR Science correspondent Richard Harris at rharris@npr.org.

81. Korley FK, Durkalski-Mauldin V, Yeatts SD, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswall S, Kaplan A, Lowell E, Mcdyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLM, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit R, Barsa W, Callaway CW, for the SIREN-C3PO Investigators: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

What follows is what I wrote two years regarding this study and it is just as relevant today as it was then. Much of my analyses and discussions in the spiral bound book (references 12-14 +), references 7,9,10, and my correspondence with the NIAID, FDA, and The White House are linked to Korley, et. al.: Early convalescent plasma for high-risk outpatients with COVID-19, N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] and its Supplement.

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

> The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include **NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O.** In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and **NOT** by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

> Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960.

https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the Supplementary Appendix which is very important can be found at (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf).

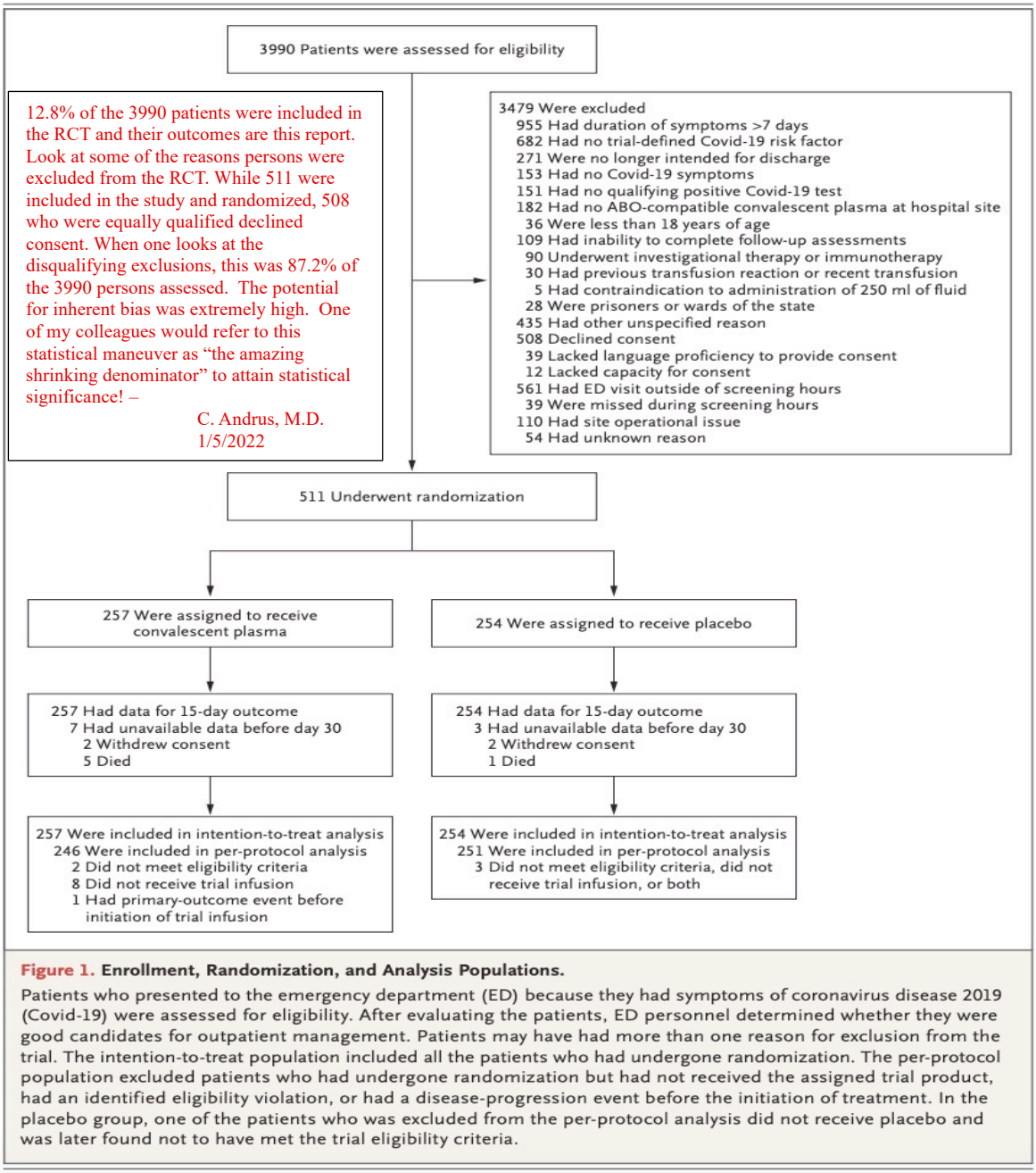
3990 Patients were assessed for eligibility
12.8% of the 3990 patients were included in the RCT and their outcomes are this report. Look at some of the reasons persons were excluded from the RCT. While 511 were included in the study and randomized, 508 who were equally qualified declined consent. When one looks at the disqualifying exclusions, this was 87.2% of the 3990 persons assessed. The potential for inherent bias was extremely high. One of my colleagues would refer to this statistical maneuver as "the amazing shrinking denominator" to attain statistical significance! –
C. Andrus, M.D.
1/5/2022
3479 Were excluded
955 Had duration of symptoms >7 days
682 Had no trial-defined Covid-19 risk factor
271 Were no longer intended for discharge
153 Had no Covid-19 symptoms
151 Had no qualifying positive Covid-19 test
182 Had no ABO-compatible convalescent plasma at hospital site
36 Were less than 18 years of age
109 Had inability to complete follow-up assessments
90 Underwent investigational therapy or immunotherapy
30 Had previous transfusion reaction or recent transfusion
5 Had contraindication to administration of 250 ml of fluid
28 Were prisoners or wards of the state
435 Had other unspecified reason
508 Declined consent
39 Lacked language proficiency to provide consent
12 Lacked capacity for consent
561 Had ED visit outside of screening hours
39 Were missed during screening hours
110 Had site operational issue
54 Had unknown reason
511 Underwent randomization
257 Were assigned to receive convalescent plasma
254 Were assigned to receive placebo
257 Had data for 15-day outcome
7 Had unavailable data before day 30
2 Withdrew consent
5 Died
254 Had data for 15-day outcome
3 Had unavailable data before day 30
2 Withdrew consent
1 Died
257 Were included in intention-to-treat analysis
246 Were included in per-protocol analysis
2 Did not meet eligibility criteria
8 Did not receive trial infusion
1 Had primary-outcome event before initiation of trial infusion
254 Were included in intention-to-treat analysis
251 Were included in per-protocol analysis
3 Did not meet eligibility criteria, did not receive trial infusion, or both

Figure 1. Enrollment, Randomization, and Analysis Populations.

Patients who presented to the emergency department (ED) because they had symptoms of coronavirus disease 2019 (Covid-19) were assessed for eligibility. After evaluating the patients, ED personnel determined whether they were good candidates for outpatient management. Patients may have had more than one reason for exclusion from the trial. The intention-to-treat population included all the patients who had undergone randomization. The per-protocol population excluded patients who had undergone randomization but had not received the assigned trial product, had an identified eligibility violation, or had a disease-progression event before the initiation of treatment. In the placebo group, one of the patients who was excluded from the per-protocol analysis did not receive placebo and was later found not to have met the trial eligibility criteria.

In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate

in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum ß that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: …for the SIREN-C3PO Investigators* where the "*" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

> Has at least one study defined risk factor for severe COVID-19 illness:
>
> Age ≥ 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. **Characteristics of the Patients at Baseline**:

Characteristic	**Convalescent Plasma (N=257)**	**Placebo (N=254)**
Median age (IQR)	54 (42-62)	54 (40-62)

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participattion in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes?

82. **2020-03-05. YouTube: Regeneron's Leonard S. Schleifer meets with Trump at the White House, 3/2/2020. https://www.youtube.com/watch?v=31i6p_stzW8 AT THIS MEETING, PRESIDENT TRUMP AND ALL THE PEOPLE OF THE WORLD WERE MISLED BY OMISSION / MISREPRESENTING THE DISTINCTION BETWEEN *ACTIVE IMMUNIZATION (vaccines)* versus *PASSIVE IMMUNIZATION (convalescent plasma, convalescent sera, monoclonal antibodies, monoclonal antibody cocktail, etc.)*.** The cost of production of a dose (1/2 unit of fresh frozen plasma) COVID-19 Convalescent Plasma (CCP) which was available in March 2020 is ~$200 while a dose of REGEN-COV™ (Casirivimab with imdevimab) which would be several months into the future and would cost ~$3000 a dose. A monoclonal antibody is specific for one antigen (e.g. a specific site on the spike point) and is likely to be ineffective on future variants like Omicron. Polyclonal antibodies like Convalescent Plasma will have multiple antibodies of such sites as on the spike protein and will be available as the SARS-CoV-2 mutates. (e.g. more effective on the Omicron variant).

***** **Full 56:54 minute meeting in *The White House* where they went around the table introducing the key players: https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus with the complete transcript: https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/** This **linchpin** *White House* meeting included CEOs, presidents, and Medical Directors of the major biomedical and pharmaceutical companies who could provide vaccines, monoclonal antibodies, and antivirals; the Secretary of the U.S. Department of Health and Human Services and its agencies (e.g.: FDA, NIH, CDC, etc.); and the Vice-president and the President of the United States of American. 1.) Nobody defined the foundational basics of Clinical Immunology: Active Immunization and Passive Immunization. 2.) Everything was in Generalities – NOT THE INDIVIDUAL PATIENT! 3.) The not-for-profit American Red Cross was *NOT* officially invited "to the table" until July 30, 2020—by that time, the U.S.A. had gone so far down the Rabbit Hole, they did not know how to get out! 4.) No physician in that room, on that day, has probably cared for the individual patient since Medical School.

Individuals at the White House meeting of March 2, 2020.

President Donald Trump, 2 years Fordham University and the 2 years Wharton School of the University of Pennsylvania, B.S. in Economics

Alexander Azar, Secretary of the U.S. Department of Health and Human Services, summa cum laude in government and economics from Dartmouth and J.D. from Yale University

Emma Walmsley , CEO of GlaxoSmithKline, MA in Classics and Modern Languages from Oxford University (Christ Church)

Anthony Fauci, M.D., Director of the NIAID of the NIH, College of the Holy Cross with a BA in classics and a MD from Cornell University graduating 1st in his class

Robert Redfield, M.D., Director of the CDC, graduated from Georgetown University's College of Arts and Sciences with a BS and MD from Georgetown University School of Medicine

Daniel Menichella, CEO of CureVac, BA in economics from Harvard University and a MBA from University of North Carolina at Chapel Hill

John Shiver,PhD, Senior Vice President, Vaccines Global R&D at Sanofi Vaccines, BS in Chemistry/Mathematics, Woffard College and a PhD in Chemistry from the University of Florida

Leonard Schleifer, M.D., PhD, CEO Regeneron, BS at Cornell University and an MD-PhD from the University of Virginia

Stephane Bancel, CEO of Moderna, masters degrees from both CentraleSupélec of Paris-Saclay University (engineering) and the University of Minnesota (biological engineering) and an MBA from Harvard Business School

Daniel O'Day, BS, MBA, Chairman and CEO of Gilead Sciences has a BS in biology from Georgetown University and an MBA from Columbia University in New York

Steven Hahn, M.D., Commissioner, U.S. Food and Drug Administration, BA in Biology from Rice University and MD from Temple University

Mikael Dolsten, M.D., Ph.D., Chief Scientific Officer of Pfizer, Ph.D. in tumor immunology and a MD from Lund University

Joseph Kim, Ph.D., Inovio Pharmaceuticals, BS degrees in Chemical Engineering and Economics from MIT, a Ph.D. in immunology from the University of Pennsylvania, and an MBA in finance from the Wharton School of Business, University of Pennsylvania

Paul Stoffels, M.D., Chief Scientific Officer of Johnson & Johnson, studied medicine at the University of Diepenbeek and the University of Antwerp in Belgium and Infectious Diseases and Tropical Medicine at the Institute of Tropical Medicine in Antwerp, Belgium.

Anne Schuchat, M.D., Principal Deputy Director of the CDC, Swarthmore College and MD Dartmouth Medical School

Stanley Erck, President and CEO of Novavax, undergraduate degree from the University of Illinois and MBA in economics and finance from the Booth School of Business, The University of Chicago

Ambassador Deborah Birx, M.D., U.S. Department of State, BS in chemistry from Houghton College and MD from Pennsylvania State University.

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Attachment II: List of Accompanying Documents to Dr. Andrus' response letter of March 4, 2024, to President Joseph Biden in Dr. Andrus' response to President Biden's letter of July 7, 2023

Dear Reader, Please note that March 4, 2024, was the 159th year anniversary day of President Abraham Lincoln's second inaugural address in which he promised from all of us for all times:

…to care for him who shall have borne the battle, and for his widow and his orphan…

Book 1: Andrus CH: *Book 1: Dear Mr. President: COVID-19 and Where We Went Wrong 2023 02 02*. Internet Archive, uploaded: 2023-09-12, pages: 1 - 1266. NIH NIAID Case #12276. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02/

[*Description:* This is a copy of Book 1: Dear Mr. President...COVID-19 and Where We Wrong first submitted to agencies of the DHHS, the DVA, and the President of the United States in September 2022. It has been edited over the last year but is still in draft form. What is more, the submission to the Internet Archive is for NO personal financial gain. As a former VHA physician and surgeon of the U.S. Department of Veterans Affairs, it is (1) my duty as a former federal physician and (2) mandate to the oath I swore professing *Primum non Nocere,* that today, I submit this to the American people as a purely educational contribution that should be debated, analyzed, and appropriately acted upon by U.S. Medicine, the FDA, the NIH, the NIAID, the VA, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.]

Book 2: Andrus CH: *0 2023 09 11 Scan VA RSSO Case 286816 Letter Arrived Feb 13 2023*. Internet Archive, uploaded: 2023-09-11. NIH NIAID Case #12276. Pages 1-3 plus 5 additional attached .pdf files:
https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/0%202023-09-11%20scan%20VA%20RSSO%20Case%20286816%20letter%20arrived%20Feb%2013%202023/

Pages 1-3:

[*Description:* This is the final cover letter from the VA Workforce Management & Consulting (WMC), Retirement Shared Service Office (RSSO), VA RSSO Case #286816 received by Dr. Andrus on Feb 13, 2023, with the 18 lbs of documentation submitted by Dr. Andrus on January 30, 2023 per the request of the VA RSSO. The fourth paragraph inappropriately closed the door on the recalculated back pay of ~$82,000 owed to Dr. Andrus and revision of his monthly pension by: "...after speaking with leadership, it was determined to return the documents you have mailed in as they are not pertinent to your salary discrepancy or the retirement."]

The five additional .pdf files attached to this Internet Archive upload.

01 2023-01-29 cover Andrus e-mail transmission to VA.pdf https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/01%202023-01-29%20cover%20Andrus%20e-mail%20transmission%20to%20VA%20/

03 Appendix C VA Commendations Andrus 2023-01-28.pdf https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/3%20Appendix%20C%20VA%20Commendations%20Andrus%202023-01-28/page/n3/mode/1up

04 Appendix D Andrus 2023-01-29.pdf. https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/4%20Appendix%20D%20Andrus%202023-01-29/

05 SF-50s including 01-19-2002 45.remarks Constructive Discharge.pdf. https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/5%20SF-50s%20including%2001-19-2002%2045.remarks%20Constructive%20Discharge/

06 1999-11-12 VA OIG report Hines VAH CAP 99-00173-18 https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/6%201999-11-12%20VA%20OIG%20report%20Hines%20VAH%20CAP%2099-00173-18/ This file is only a space filler as the VA OIG Website URL has been removed by the VA of: https://www.va.gov/oig/pubs/99-00173-18 Therefore, I uploaded to the Internet Archive a copy of the VA

Office of Inspector General's: *Combined Assessment Program Review, Edward Hines, Jr. VA Hospital, Hines, IL,* Report No. 99-00173-18, Date: November 22, 1999 to:

06.3005 1999 11 22 Hines VAH CAP 99 00173 18 Copy Charles H. Andrus, M.D., F.A.C.S. uploaded as this VA OIG report was published for PUBLIC RELEASE by the U.S. Department of Veterans Affairs, Office of Inspector General on November 22, 1999. Internet Archive, upload March 2, 2024. https://archive.org/details/06.3005-1999-11-22-hines-vah-cap-99-00173-18-copy

Topics: U.S. Department of Veterans Affairs, Office of Inspector General, CAP Review, Edward Hines, Jr. VA Hospital, Report No. 99-00173-18, November 22, 1999, https://www.va.gov/oig/pubs/99-00173-18.pdf

[Description:

The VA OIG website for the Hines VAH CAP 99-00173-18 has been removed from the VA OIG Website URL: https://www.va.gov/oig/pubs/99-00173-18.pdf which today yields: "Sorry, we can't find that page"; and this VA OIG Website URL was never uploaded to the Internet Archive over the last 25 years. Thus, on 3/2/2024, I uploaded in a .pdf format a scanned copy of the complete VA OIG report No. 99-00173-18 of November 22, 1999, signed off by Richard J. Griffin, DVA Inspector General, which was 48 pages in length: title page, i-v, 1-42. This scanned copy is contained in its entirety in Chapter 6 of the—as yet, not uploaded-- unabridged Book 3, pages 192-259: 06.3005 1999-11-22_Hines_VAH_CAP_99-00173-18.pdf.

In October/November 1999, roughly 4 weeks prior to the publication of this report by the VA OIG, a young man from the regional IG office on the Hines VAH grounds presented to my Hines VAH office on the fifth floor of Building 200 and asked if I had any documentation of OR resident supervision at the Hines VAH. I, immediately, provided him with a 3 ½" diskette which contained the latest monthly report on resident supervision by surgical specialty never realizing that the VA OIG would publish it. It consisted of: A monthly cover letter on Attending Surgeon supervisory levels of residents and an Excel data base entitled Surgery Resident Supervision in OR—FY 99 (the last 17 pages of APPENDIX IV, pages 43-61 of 99-00173-18). (An abridged version of this report can be found on pages 277-283 of Book 3: https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-the-battle-2024-02-29/ . While the title page states VA OIG report No. 99-00173-18 was **FULLY-REDACTED**, the VA OIG did not redact my name from the cover letter as I was one of the two named signatories on page 44 of the report. (This VA OIG official report confirms I existed as the Chief of Surgery, Edward Hines, Jr. VA Hospital, Hines, IL on October 14, 1999, which contradicts the official search of the U.S. National Archives for the existence of my Official Personnel File (OPF) from 1982 to 2002 as is documented on page 533 of Book 3 https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-the-battle-2024-02-29/ .)

In the letter on page 1 of Book 2: Andrus CH: *0 2023 09 11 Scan VA RSSO Case 286816 Letter Arrived Feb 13 2023*. Internet Archive, uploaded: 2023-09-11. https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/0%202023-09-11%20scan%20VA%20RSSO%20Case%20286816%20letter%20arrived%20Feb%2013%202023/ it is stated by the RSSO official: "**…In addition, after speaking with leadership, it was determined to return the documents you have mailed in as they are not pertinent to your salary discrepancy or the retirement."**

When I resigned from the VHA in January 2002, my Grade and Step was 15-10. When I returned to the VHA in August 2016, I was designated by the VHA as a Physician and Surgeon as a 15-07, a *de facto* demotion, as there reportedly was no confirmation of my 18 years of service in the VHA from 1982-2002. As is documented on page 4 of 3 Appendix C VA Commendations Andrus 2023-01-29 https://archive.org/details/0-2023-09-11-scan-va-rsso-case-286816-letter-arrived-feb-13-2023/3%20Appendix%20C%20VA%20Commendations%20Andrus%202023-01-

28/page/n3/mode/1up , I retired with 25 years of service which under Title 38, U.S.C. Sec. 7431, qualified me to be the rank of Grade 15 Step 13 (instead of Grade 15 Step 10). *Res ipsa loquitur*: I should have a retirement rank of Grade/Step of 15-13, my calculated outstanding back pay is ~$82,000, and my retirement pension should be recalculated by the RSSO of the DVA for the last 6 years of my VHA service from 2016 – 2022 as my Step and Grade should have been from 15-10 to a 15-13 (Not 15-7 to 15 – 10).
Respectfully,
Charles Andrus, M.D., F.A.C.S.]

Book 3: Andrus CH: *Abridged Dear Mr. President: "…to care for him who shall have borne the battle…"*A. Lincoln Internet Archive, uploaded: 2024-02-29, pages 1-534. NIH NIAID case #12276 https://archive.org/details/book-3-abridged-dear-mr-president...-to-care-for-him-who-shall-have-borne-the-battle-2024-02-29

Topics: IL-372, PATH, Physicians at Teaching Hospitals, Veterans Health Administration, Resident Supervision, to care for him who shall have borne the battle

[*Description:* This is an abridged version of the yet to be uploaded Dear Mr. President...To Care for Him Who Shall Have Borne the Battle...A. Lincoln which is a composite (of > 3500 pages) of this abridged version of Book 3--A confirmatory chronological compendium of primary sources and resultant correspondence between Dr. Andrus and:

(1) the U.S. Department of Veterans Affairs [VA OIG 2000 HL-0347, 9HL-015, U.S. DVA ORM/EEO 200k-1886; U.S. EEOC 03A20075, 210-A2-6164X, 210-A3-6145X, etc.],
(2) the U.S. Merit Systems Protection Board,
(3) the EEOC,
(4) the U.S. Court of Appeals for the Federal Circuit, docket case #03-3162,
(5) the Veterans Affairs Committee of the U.S. House of Representatives,
(6) the U.S. Office of Special Counsel [MA-00-1107, DI-00-1147],
(7) the U.S. Department of Justice, (8) The White House,
(9) Academic and Research Medical Organizations and Medical Societies (e.g.: the CDC, AMA, ACS, NIH NIAID case #12276 between 2020 - the present, etc.) and the staffs of the NEJM, JAMA, American Journal of Surgery, etc.,
and other academic and research entities of American Medicine.

The central issue of this book covering over 5 decades is allegations of **the *de facto* denial of care, the *de facto* dereliction to duty, and the *de facto* disregard of patients' rights by some Teaching Physicians and Surgeons in the condoning of Ghost Surgery for a half-century.** (Ghost Surgery: Attending Surgeon supervising but not physically being present during the performance of operations, procedures, and encounters by physicians-in-training [residents].) This book documents the misapplications by some of the Rules of Attending Surgeon Supervision as mandated in the private and public section under **Intermediary Letter 372 (IL-372)** of the Social Security Administration and in the Veterans Health Administration under **VHA Handbook 1400.1**.

Much of the subsequent correspondence is permeated with legal obfuscation and chronic denial.

Submitted respectfully as is my duty as a retired Physician and Surgeon, Veterans Health Administration, U.S. Department of Veterans Affairs,

Charles H. Andrus, M.D., F.A.C.S.

--former Chief, Surgical Services, Edward Hines, Jr. VAH, Maywood, IL (tertiary Chicago VA hospital and first VAH of the University/VA affiliation in 1946, PL 79-293), Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (1996 - 2002)

--former Professor and Vice-chairman, Department of Surgery, Loyola University School of Medicine (1996- 2001)

--retired Attending Surgeon (and for most of the time, Chief, Unit II General Surgery--Saint Louis University GS division), John Cochran (St. Louis) VAMC, Veterans Health Administration, U.S. Department of Veterans Affairs (1986 - 1996) and (2016 - 2022)

--retired Professor and Surgeon, Department of Surgery, Saint Louis University School of Medicine (2006 - 2022); Medical Student: 1975 - 1979, Pediatric Resident: 1979 - 1981, General Surgery Resident: 1981 - 1986, faculty: 1986 - 1996, 2006 - 2022.

Book 4: Andrus CH: *Book 4: Biden Response to The Summary of Book 1 COVID 19 And Where We Went Wrong.* Internet Archive, Uploaded 2024 Feb 05, **[Only 382 pages loaded]** https://archive.org/details/book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong/ , ***** Uploaded again on March 5, 2024 to the Internet Archive and all 848 pages were uploaded. Title: 0.4 Book 4 Biden response to the Summary of Book 1 COVID 19 And Where We Went Wrong 2nd Attemp , *Internet Archive* , uploaded March 5, 2024.** pages 1- 848 https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp *** NIH NIAID Case #12276

[Description: On July 7, 2023, President Joseph Biden replied to the included summary submission of Book 1: Dear Mr. President: COVID-19 and Where We Went Wrong. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02/

NIH NIAID Case#12276. Book 1 is 1266 pages documenting correspondence with the NIAID, the FDA, the VA, and The White House over 3 years concerning the clinical care of patients newly infected with COVID-19. All the documentation that has been submitted to the NIHNIAID Case #12276

(Book 1 is an abridged documentation) is available through the Freedom of Information Act Officer of the NIAID. The submissions to the NIAID and FDA in detail outlined the pathophysiology of coronavirus SARS-CoV-2; the difference between Active Immunization (vaccination for PROPHYLAXIS to stimulate endogenous immunoglobulins) vs Passive Immunization in the TREATMENT of acute COVID-19 [within 72 - 120 hours of diagnosis] through the administration of exogenous immunoglobulins, e.g.: Convalescent Plasma, Monoclonal Antibodies, and Monoclonal Antibody cocktails, etc.); describe extreme misinformation and obfuscation by the NIH, NIAID, FDA, etc.; describe in-depth the inappropriate late timing of administration of immunoglobulins and antivirals (>120 hours from diagnosis of acute infection); and the cover-up by governmental, academic, etc. entities by electronic overwriting, URL site relabeling/renaming, and website removal; officials, medical researchers, academics, and clinicians, and agencies advancing incorrect or misleading medical statistics and theories that were associated with and were possibly contributory to >1,000,000 reported deaths from COVID-19 in the U.S.A. from March 2020 to the present. -- Charles H. Andrus, M.D., F.A.C.S.]

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>
> > **(3) Level 3.** The staff practitioner is immediately available in the facility – campus for direct resident supervision according to local policy as approved by the Network Academic Affiliations Officer. The service chief is responsible for periodically reviewing cases done under Level 3 supervision to ensure that such supervision is appropriate.
>
> Using the Wayback Machine another version of the Level 3 Supervision (now Level D) is identified: In VHA Handbook of July 27, 2005 signed by Jonathan B. Perlin, M.D. https://web.archive.org/web/20051107072236/http:/www.va.gov:80/OAA/1400_1hk_July27_05.doc (Recission of the previous version of May 3, 2004 which cannot be found):
>
> > 4. **Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and immediately available for resident supervision or consultation as needed.

Using the only other "hit" on the Wayback Machine of December 21, 2016, http://web.archive.org/web/20161221045318/http://www.va.gov/oaa/1400_1hk_Oct2001.doc VHA 1400.1 has been removed completely and in its place is the website of the U.S. Department of Veterans Affairs which states: "Page Not Found." ***De facto*, the U.S. DVA, VHA**

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38. Petzel RA: Resident Supervision. VHA Handbook 1400.01, Veterans Health Administration, U.S. Department of Veterans Affairs, 19 Dec 2012 https://www.va.gov/OPTOMETRY__/docs/VHA_Handbook_1400-01_Resident_Supervision_12-19-2012.pdf

> **5. RECISSIONS.** VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005 is rescinded……. (page 1). [***Please note that when one searches for VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005, one is redirected to VHA Handbook 1400.01. Using the Wayback Machine and the previous URL for VHA 1400: http://web.archive.org/web/20161221045318/https://www.va.gov/oaa/1400_1hk_Oct2001.doc , one can find the 2001 version in the 2004 of the Internet Archive captures. There are no other captures of this URL in the Wayback Machine except December 21, 2016 which brings up the VA Website which states: "Page Not Found."***
>
> **4. Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and able to provide direct supervision or consultation without delay as needed. (page 9)

39. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063, Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. The original version of VHA Directive 1063 of December 24, 2013 which claimed physician assistants could be independent practitioners -- which I would allege is a violation of every State Medical Boards' credentialling policies/laws regarding Physician Assistants. In the 2013 version, the justification of the violation of all State Medical Boards was in 2.c:

> Under the Supremacy Clause of the U.S. Constitution, States are prohibited from regulating or controlling the activities of the Federal Government without written Congressional consent; where Federal and State laws conflict, Federal law governs official actions of Federal employees. Examples of the types of activities that the Federal Government may establish are qualifications for employment and scopes of practice. Therefore, the establishment of scopes of practice for VA PAs defined by this Directive is without regard to State Practice Acts.
> https://web.archive.org/web/20140814150238/https:/www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958

40. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063 (1), Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. Captured on July 22, 2023, by the *Internet Archive.* https://web.archive.org/web/20230722070741/https://www.va.gov/VHAPUBLICATIONS/ViewPublication.asp?pub_ID=2958 In **2. SUMMARY OF CHANGES** of the **Transmittal Sheet** which is still labelled **December 24, 2013** but in red has stamped: **AMENDED May 17, 2022** is: (1) Paragraphs 2.c. and 2.e. removes references to the Supremacy Clause reference and physician liability.—which means that the independent practice of a VHA Physician Assistant was rescinded returning all Physicians Assistants to the State Medical Board statutes outlining mandatory Physician scope of practice affiliations and legally mandated Physician oversight. The signatory official on this document is Robert A. Petzel, M.D., Under Secretary for Health who had been terminated over the Phoenix VAMC scandal 8 years prior to this as noted above in references 36 and 37.

41. Petzel RA: Utilization of Physician Assistants (PA) VHA Directive 1063(2), December 24, 2013 AMENDED June 24, 2024. When one uses a search engine like GOOGLE or enters the official URL of this document site: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 , one is electronically shifted to a .pdf file, e.g.: file:///Users/andrusmd1/Downloads/1063(2)_D_2013-12-24%20(6).pdf. The https://... URL version was captured by the *Internet Archive* on July 18, 2024. The signatory official on this document is still Robert A. Petzel, M.D., Under Secretary for Health, who had been terminated over the Phoenix VAMC scandal 10 years prior to this as noted above in references 36 and 37. https://web.archive.org/web/20240718212213/https://www.va.gov/VHApublications/ViewPublication.asp?pub_ID=2958

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> After OIG Inspector Griffin's testimony on May 8, 2003, ABC *Primetime* investigated for an entire year and on April 8, 2004, aired Fighting for Care narrated by Diane Sawyer. 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212) This episode was removed from the ABC Archives possibly because ABC to hidden cameras into the Cleveland and Temple, TX VAMCs. 2004 George Polk Award for "**Television Reporting: Diane Sawyer** and **Robbie Gordon**, ***ABC News PrimeTime Live***, for **"Fighting for Care,"** which documented patient abuse and deplorable conditions in VA hospitals." (for investigative reporting excellence) https://liu.edu/polk-awards/past-winners#2004. When Tammy Shehari, the Associate Producer for the episode, spoke with me by phone in 3/2004, she asked me to estimate how many additional veterans had died due to unsupervised operations performed by Surgery Residents– I declined to guess because to do so would be wrong and a disservice to the Veteran patients and the men and women of Department of Veterans Affairs that do their duty faithfully for Veteran patients. (The interview ended shortly after my refusing to guess, and this was the only time ABC News spoke with me.)

Please note the reference above -- VHA USH, Robert Roswell, M.D. resigned three days prior to the airing of *Fighting for Care*. *Fighting for Care* contained within unauthorized hidden cameras in the Cleveland VAMC and the Temple TX VAMC. The VA spin was: …Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. …. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

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>
> Prior to the use of antibiotics, antibodies were the only specific agents for the treatment of certain infections. Although this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1). Since several excellent reviews are available, this article will emphasize new developments (30, 31, 101, 164, 165).
>
> Antibodies can be administered as human or animal plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or convalescing donors, and as monoclonal antibodies (Mab) (30, 164,178). The therapeutic use of Mab is increasing dramatically, but only one (palivizumab for respiratory syncytial virus [RSV]) has been licensed for prophylaxis of an infectious disease.

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Footnote at bottom of every page of this Annotated Bibliographic Timeline:

---------- May 30, 2022 ---------- 3

This is a COVID-19 Timeline Bibliography for Educational Purposes *ONLY* in the presentation of this information before the people of the United States of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

This submission is NOT for financial gain but for educational purposes only for ALL the American people

This is only a scanned copy of the face sheet to President Biden of 01/18/2025. All that follows can be found in: *Book 5 Summary to President Biden 1-18-2025* that will be uploaded to the *Internet Archive*

150 Emerald Green Ct
St. Louis, MO. 63141
314-455-9482
candrus600@aol.com

NIH NIAID #12276

January 18, 2025

President Joseph Biden
The White House
1600 Pennsylvania Avenue NW
Washington, DC. 20500

Dear President Biden:

As a former Physician and Surgeon of the U.S. Department of Veterans Affairs and Professor of Surgery, Saint Louis University School of Medicine, I have attempted to communicate with the NIH, the FDA, the VA, and *The White House* regarding **early treatment** (within 72 hours of diagnosis of COVID-19 infection) in deference to prophylaxis (vaccination) for COVID-19. On July 7, 2023, you responded with the following letter: https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp

While it was a very kind acknowledgment letter, the issues I raised within U.S. Medicine remain unaddressed. Thus, attached with this cover letter is a first draft of my planned submission to *The New England Journal of Medicine*. [USPS Tracking# 9405 5036 9930 0739 9678 19] While the Editors may or may not accept it for publication, I see it as my duty to U.S. Medicine and our country to submit it.

Respectfully,

Charles Andrus MD

Charles Andrus, M.D., F.A.C.S.

Name	Date Modified	Size	Kind
0.1 2025-01-18 Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals	Today at 9:41 AM	10.3 MB	Microso...(.docx)
0.2 Attachment I Euphemistical Obfuscation in Clinical Medicine	Dec 13, 2024 at 5:52 AM	301 KB	Microso...(.docx)
0.3 Attachment II Submissions to the Internet Archive	Dec 13, 2024 at 5:55 AM	273 KB	Microso...(.docx)
0.4 Attachment III Reductio ad Absurdum	Dec 13, 2024 at 5:57 AM	4.8 MB	Microso...(.docx)
0.5 Attachment IV Validation letter from the NIH NIAID establishing NIAID Case # 12276	Dec 13, 2024 at 6:17 AM	8.7 MB	Microso...(.docx)
0.6 Attachment V 1977 NEJM letter of Case of Chronic Denial with Alfred Gilman response	Dec 13, 2024 at 6:03 AM	921 KB	Microso...(.docx)
0.7 Attachment VI Tables re Sources Definitions and Statistics	Dec 13, 2024 at 6:06 AM	627 KB	Microso...(.docx)
0.8 Attachment VII Letters to Members of Congress and Pres Trump 8_23_2020 and 8_28_2020	Dec 12, 2024 at 10:20 AM	3.4 MB	Microso...(.docx)
0.9 Attachment VIII 08 076.0 2021-09-19 Tragedy of Electronic Overwriting	Dec 31, 2024 at 11:29 AM	635 KB	Microso...(.docx)
1.0 REFERENCES of ATTACHMENTS I - VIII	Dec 13, 2024 at 11:48 AM	264 KB	Microso...(.docx)
2.1 Table 1- Digital vs. Analog—Yes, No, Maybe in Medicine and Treatment of Covid-19	Dec 13, 2024 at 6:33 AM	2.1 MB	Microso...(.docx)
2.2 Definitions_Fundamentals_Legal_Mandates background	Dec 13, 2024 at 6:13 AM	33 KB	Microso...(.docx)
2.3 2024-11-23 Tables 2-6	Dec 12, 2024 at 10:44 AM	5.9 MB	Microso...(.docx)
2.4 References for Tables 1 – 6	Dec 13, 2024 at 6:39 PM	2.1 MB	Microso...(.docx)
3 2024-11-23 Some Pertinent Transcripts and Excerpts	Nov 23, 2024 at 6:25 AM	2.9 MB	Microso...(.docx)

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Generalized Dismissal of Early Treatment with *Passive Immunization* and Antivirals (Not Prophylaxis/*Active Immunization*) in Persons Infected with COVID-19

Charles H. Andrus, M.D., F.A.C.S.
Former Professor (Tenured), Department of Surgery, Saint Louis University SOM
Former Professor and Vice-Chairman, Department of Surgery, Loyola University SOM and Chief, Surgical Services, Edward Hines, Jr. VAH
Former Federal Whistleblower at the direction of the VA OIG and VHA Medical Inspector – U.S. Office of Special Counsel, files MA-00-1107, DI-00-1147
U.S. Court of Appeals for the Federal Circuit, *Andrus v VA*,
Case# 03-3162 (EEOC case 210A36145X)
NIAID Case #12276, U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)

Correspondence: Charles H. Andrus, M.D.
150 Emerald Green Ct
St. Louis, MO. 63141
314-265-1814

Draft of January 18, 2025

Abstract:
Introduction: On March 2, 2020, in the Cabinet Room, *The White House* COVID-19 Commission was announced establishing a collaboration among the Commission, key-players in U.S. Medicine, and the Pharmaceutical and Biological Companies. Throughout America's four years of addressing the COVID-19 epidemic before the public, official plans based on future prophylaxis of the population (Active Immunization) were promoted as paramount in deference to the immediate treatment of all COVID-19-infected individuals within 72 hours of diagnosis during the viremic phase of the disease with immunoglobulins (Passive Immunization) and antivirals. During March and April 2020, a series of misdirected assertions resulted in a confused, arbitrary, bureaucratic, leaderless methodology: (1) non-sensical euphemistic definition of *"Passive Vaccination"* (3/2/2020); (2) Public Health Emergency declaration (3/13/2020); (3) *de facto* suspension of individual patient's rights under EMTALA (3/17/2020); (4) the Surgeon General's PSA advising infected patients to avoid hospitals (3/18/2020); (5) instead of designating COVID-19 Convalescent Plasma (CCP) as biosimilar biologic to Fresh Frozen Plasma (FFP), the FDA designated CCP as Investigational (3/24/2020) and incorrectly established "eligibility criteria" resulting in *de facto* rationing CCP (and all other treatments) from most of the acutely infected population; (6) with the electronic overwriting of the 3/24/2020, the FDA, the NIH, and the VA implement across-the-board the subliminal practice of electronic overwriting and URL sunsetting which are broad violations of the Sarbanes/Oxley Act of 2002, 18 U.S.C. §1512(c)(1); and (7) the initiation of the FDA/Mayo Clinic CCP Express Access (***Compassionate Use***) Program (4/1/2020) (with mainly >100,000 treatments during the late-in-disease/non-viremic phase) thus precluding official completion of Phase I safety studies and preventing individual-infected patient's rights to ask for CCP off-protocol under The Right to Try Act of 2018, PL-115-176, 21 U.S.C. 360bbb-0a.

Methods: (1) The vast majority of documentation covered by this summary paper was submitted to NIH NIAID case file #12276 which was established in a response letter of 6/10/2020, directed by Dr. Fauci is discoverable under the Freedom of Information Act, 5 U.S.C. 552. (2) In-depth summaries —especially Books 1, 3, & 4-- can be found by a search of the *Internet Archive Advanced Search* by entering **VA** in "Any field" and **Charles Andrus** in "Creator". (3) Examples of the illegality of Electronic Overwriting and URL sunsetting as violations of the Sarbanes-Oxley Act of 2002, 18 U.S.C. §1512(c)(1) are delineated throughout this paper. (4) Fact checking and identifying misstatements, misinterpretations, and misrepresentations of official definitions that have resulted in *paltering* defilements, violations of Federal law, and lies of commission and omission are key components of the Results and Discussion sections of this paper. (5) Statistical analyses were performed on (a) the *ex post facto* November 18, 2021 *NEJM* article: Korley, *et al.*: Early convalescent plasma for high-risk outpatients with Covid-19 and (b) the FDA documentation of improved survival reports due to CCP when administered early-in-the-individual's disease-course of August 23, 2020 and September 23, 2020, contradicting (c) the FDA subliminal withdrawal of CCP availability and usage subsequent to the NIH funded SIREN-C3PO report without credible background documentation of March 2021.

Results: Korley, *et al*, of November 2021, published in the *New England Journal of Medicine* is a misleading, *post facto*, statistically corrupt analysis of the early administration of CCP (within 72 hours of diagnosis of COVID-19 in the individual patient) as was put forth in March 2021, from the NIH funded SIREN-C3PO randomized controlled study without documentation at that time. The FDA documentation on August 23, 2020 and September 23, 2020, correctly reported that when CCP was given to ≤80 year-old patients within 72 hours of new COVID-19 documentation, there was significant decreased mortality and increased survival in all those treated.

Discussion: Flagrant electronic overwriting of official governmental polices and documentation and discontinuation of direct access to URLs regarding critical points in the administration of *Passive Immunization* (CCP) and antivirals within 72 hours of diagnosis of COVID-19 infection led to rejection of long-term, foundational clinical therapeutic guidelines. With regards to the presentation of all future novel viruses, U.S. Medicine has incorrectly rewritten history and condemned our society to a focus on only prophylaxis (*Active Immunization*) and not immediate treatment to all infected with a novel virus.

Introduction:

With the onset of the world-wide COVID-19 pandemic, the vast majority of countries were affected throughout the course of 2020-2022 with a prevalence and mortality of each country decreasing approaching an asymptotically long-term endemic nadir. While important (but-treatment-distracting) debates raged throughout the World regarding (Personal Protective Equipment) PPE[1,2], isolation / quarantine methodologies[3], and therapeutic supportive care.[4] The underlying medical urgency throughout the world was the immediate development of effective therapeutics for (1) the treatment of the acutely infected individuals and (2) prophylaxis for the future across all populations.[5-9] Unfortunately, the focus in the United States publicly became an almost exclusive emphasis on prophylaxis—***Active Immunization*** / vaccination[10-14] euphemistically[15] confusing vaccine prophylaxis with treatment with ***Passive Immunization*** and ***Antivirals*** of active disease bordering on subliminal infected-patient abandonment.

One of the first officially public meetings by the government, medical academia, and pharmaceutical industry to address the pending COVID-19 American epidemic occurred in the Cabinet Room of the *The White House* on March 2, 2020.[16] In attendance were President Donald Trump, Vice-President Michael Pence, and some prominent representatives from U.S. Medicine, Academia, and Pharmacologic and Biologic Companies. **(Transcript 3)** The uniquely historical, traditionally-indispensable groups usually in the forefront in the combating of an epidemic of an immunologically-novel virus that was absent from that meeting of March 2, 2020, were representatives of the Association of American Blood Banks (AABB) and the American Red Cross (ARC).[17-21] As in the early stages of several epidemics of immunologically-novel viruses during the 20th century, the AABB and the ARC should have become immediately the initial facilitators of the collection, processing, and distribution immunotherapy as an early treatment (< 72 hours from diagnosis) (not as prophylaxis) with the initial immunotherapy: convalescent plasma. A national plasma-collection-drive to provide for the stockpiling and distribution to all infected individuals within 72 hours of diagnosis with COVID-19 Convalescent Plasma (CCP)—a polyclonal *Passive Immunization* agent—should have been initiated.[22-25] Along with the declaration of a Public Health Emergency (PHE) of March 13, 2020[26], there should have been a Presidential nation-wide mandate for the collection, processing, distribution, and early treatment-administration within 72 hours of diagnosis to all individuals infected with COVID-19 with convalescent plasma (CCP) and/or serum.

Throughout the twentieth century, prompted by the scientific research investigations in the late 19th century like Pasteur's administration to Joseph Meister of the rabies vaccine (1885)[27-29] and the resultant awarding of the first Nobel Prize in Physiology or Medicine (1901) to Emil Adolf von Behring for his work on serum therapy (e.g.: against diphtheria and tetanus)[30-32], ***Passive Immunization*** has been utilized for over a century to provide exogenous antibodies: (1) in the acute treatment of viral and bacterial diseases and infectious epidemics and endemics; (2) in the neutralization of snake and insect envenomations; (3) in the prevention of sensitization of postpartum Rh negative mothers within 72 hours of delivery or miscarriage of a Rh positive child thus markedly diminishing in the mother's future possibility of delivering a subsequent offspring suffering from the major cause of hydrops fetalis in future pregnancies and thus

historically decreasing the prevalence of neonate mortality; (4) in the immunological supplementation of immunodeficient patients and in the treatment of autoimmune diseases; treatment in the attenuation of transplantation rejection; and, (5) as recurrent-monthly prophylaxis, in such viral diseases as RSV in high risk infants.[33-47]

In the approach to the treatment of acutely-infected (within <72 hours) individuals with coronavirus, SARS-CoV-2, COVID-19 in the U.S.A. as directed by U.S. Medicine (i.e.: clinical, research, and academic), though, the medical practices advocated by the U.S. Department of Health and Human Services, the U.S. Department of Veterans Affairs, and all of U.S. Medicine were essentially the nihilistic abandonment of exogenous polyclonal antibodies early (within <72 hours from diagnosis) with the ***Passive Immunological treatment*** with CCP in every acutely-infected individual. At best, this resultant confusion promoted as a massively-disorganized, leaderless disservice to the individual COVID-19 infected immunologically-COVID-19-naïve patient. A contemporary, parallel-historical, and ongoing example of this simplistic disorganization is the addressing of Respiratory Syncytial Virus (RSV) over the last quarter of a century by restricting and rationing of the monoclonal antibody palivizumab (Synagis) to only high-risk infants and neonates.[47] (**Attachment I**) U.S. Medicine's addressing of coronavirus, SARS-CoV-2, COVID-19, like RSV, is tainted throughout by ***Lies of Omission*** and ***Paltering***.[48-52]

> **PALTERING** as defined by the Merriam-Webster dictionary as: "to act insincerely or deceitfully: **EQUIVOCATE**." Probably a more contemporary, daily application in American society today would be: "***Paltering*** is the active use of truthful statements to convey a misleading impression."

A prime example of a seemingly, innocuous ***paltering*** statement at present time on television is that of Pfizer, Inc.'s aggressive marketing[53] in the American media of their *Active Immunizational* RSV vaccine, ABRYSVO:

> From this can't miss moment. To this, hello new grandfather moment. To that whatever this is moment. Your moments are worth protecting against RSV. If you're 75 or older or 60 or older with a chronic condition like asthma COPD heart disease or severe diabetes, you're at higher risk of ending up in the hospital from RSV and there are no RSV prescription treatments. Check eligibility and schedule your RSV vaccine at VaxAssist.com. Moments like this matter.
> ***Pfizer Outdo Yesterday.*** https://www.ispot.tv/ad/fA4n/pfizer-inc-your-moments-are-worth-protecting

As there are no FDA approved *prescriptive treatments* due to an *arbitrarily FDA-rationed prescriptive prophylaxis* only with the passive immunologic agent/monoclonal antibody: palivizumab (Synergis),[47] such paltering pharmaceutical marketing methodology as above[54-58] of the *Active Immunizational*, prophylactic vaccine agent, ABRYSVO, for only those >60 years old (between 2022-2024) was conjointly consistent and a continuation of the FDA's 25-year confining approvals and therapeutic restrictions / rationing of the *Passive Immunization* of the monoclonal antibody, palivizumab (Synagis). Synagis was restricted over a quarter of a century to the administration as a prophylactic regime only to non-infected, high-risk neonates and infants against Respiratory Syncytial Virus (RSV).[47] As of October 2024, this seemingly, innocuous *de facto* restrictive, rationing, collaboration between the FDA and the pharmaceutical industry has been selectively extended to promote the parasitic-marketing restriction of the RSV

vaccine Abrysvo (*Active Immunization)* to only select "high-at-risk" subgroups between 18 and 59 years of age and all those 60 years of age and over while dismissing any appropriate *Active Immunization* of the entire U.S. population regardless of age, concomitant disease, or other non-RSV conditions.[59] Coherent with what has been legally mandated for decades in all 50 states and American protectorates for all children at ages 1 and 6 years of life, the vaccination against viruses of the Paramyxoviridae family[60] by MMR inoculations (i.e.: the MMR is the vaccine against measles, mumps, and rubella)[61], is routine. Vaccination against RSV (also of the Paramyxoviridae family) in all the children would diminish, if not virtually eliminate, the vector-effect within the "herd"[62] --BUT this, at present, is not even contemplated in the United States. Failing to consider any treatment of acutely infected-RSV-individuals regardless of age with *Passive Immunization* and/or the RSV specific antiviral rabivirin[63,64] when RSV is acutely contracted by the individual patient and limiting prophylaxis with *Active Immunization* regardless of age of the entire American population is clinically ignorant and should probably be considered an unethical policy of the FDA bordering on the likes of the Tuskegee Syphilis Project—but now, at a national level.[65,66]

Throughout all walks of life, ***Paltering*** has become pervasive in U.S. society today. (**Attachment I)** The promulgation of misinformation and the disconnected distribution and marketing of disjointed, fragmented information, benefits few at the expense of many--privileged individuals, stockholders, and/or companies. ***Paltering advertising*** and ***promotion*** are overwhelmingly detrimental to society as a whole. ***Paltering*** has contributed to misinformation and ignorance of the whole whether it be in U.S. business, U.S. academia, U.S. politics, U.S. Medicine, etc. In U.S. Medicine today, our traditional safeguards (e.g.: the FDA[67,68], the CDC, the USPHS, the NIH, the VA, Academic Medicine, Editorial peer-review, etc.) that have ostensively endorsed honesty as their foundational cornerstones and tacitly promoted: *Vincit Omnia Veritas*- Truth Conquers All[69,70,Attachment VIII], **HAVE FAILED** us! In short, the American public is being treated like mushrooms -- being kept in the dark and being fed a bunch of manure (regardless how purified or rarefied it may be).[71]

In an attempt to reconcile and breach the clinical-application chasms among U.S. medical research, U.S. federal funding and support, and the daily practice of Medicine[72]—*vis-à-vis* for each and every individual patient involved in a Randomized Controlled Trial (RCT)[73-78], Dr. Jeffrey Drazen, former editor-in-chief of *The New England Journal of Medicine* has suggested a transparency in clinical trial data with availability for all.[79,80] Contradicting that which Dr. Drazen advocated in a NEJM interview[79,] regarding the NEJM's adherence to the integrity[80], this present paper is a *post-hoc*, in-depth analysis of our U.S. Medicine's obfuscation during our American COVID-19 epidemic from 2020 to the present diminishing foundational tenets in the treatment of Infectious Diseases perpetuated as ongoing misdirections throughout the COVID-19 endemic therapeutic time-line *ad infinitum*. (**2.1 Table 1**)

METHODS:

I. Historical and Legal Preservation of Data Reported over the Last 5 years: In early June 2020, consistent with the unwritten policy[81] of Dr. Anthony Fauci, M.D., Director, National Institute for Allergy and Infectious Diseases (NIAID), that:

> PS. I forgot to say there is no worry about FOIAs. I can either send stuff to Tony on his private gmail, or hand it to him at work or at his home. He is too smart to let colleagues send him stuff that could cause trouble.

Dr. Fauci requested, Kara Harris, MPH[82], Section Chief for Controlled Correspondence and Public Inquiries, Legislative Affairs and Correspondence Management Branch, Office of Communications and Government Relations, NIAID, U.S. National Institutes of Health (NIH) of the U.S. Public Health Service to respond to my communication with his office. (**Attachment IV**) Thus, Ms. Harris thanked me for my communication[82] to Dr. Fauci entitled: **Time: The Crucial *Independent Variable* of the COVID-19 Pandemic.**[84] This seemingly innocuous thank-you letter from Ms. Harris labelled my submission (and all future submissions) as NIAID Case file # 12276. On August 30, 2021, 14 months after the establishment of NIAID case file #12276 in a phone conversation[85] from "Meg" of Ms. Harris's NIAID office, NIAID case file #12276 was confirmed to still exist. This confirmation phone call to my St. Louis VAMC office phone from Ms. Harris' office was in response to my call to Ms. Harris' office earlier that morning regarding Dr. Fauci's presentation on Antibody treatment and Vaccine prophylaxis of COVID-19 from *The White House* of August 24, 2021, https://www.youtube.com/watch?v=AZNP05w2cxU (10:22 to 15:27 minutes in the youtube presentation).[86] The NIAID case file #12276 label validated the legally mandated preservation by the NIAID of all communications that was then and would be in the future submitted by me to the NIAID with the label of #12276. Thus, over the last five years, I have also included in NIAID Case file #12276 submissions to the U.S. Department of Veterans Affairs (VA), the U.S. National Institutes of Health (NIH), the U.S. Food & Drug Administration (FDA), the Centers for Diseases Control (CDC), *The White House*, etc. Some of these submissions to NIAID case file #12276 are outlined in **Attachment II**; a more inclusive, comprehensive accumulation of **Attachment II** has been uploaded to the *Internet Archive* [84,85, 87-94]; and all are protected within the NIAID and are legally discoverable under the Freedom of Information Act, 5 U.S.C. 552.[95] Consistent with federal law, 5 U.S.C. 552[95], all documents submitted to NIAID case file #12276 should be preserved, archived by the NIAID and legally discoverable "pursuant to the nine exemptions and three exclusions" listed in 5 U.S.C. 552[95] for a nominal fee set by the U.S. Government through a formal request of the Freedom of Information Act (FOIA) officer of the NIAID[96,97], NIH of the U.S. Department of Health and Human Services (DHHS). Within these submissions (posted for no personal financial gain on my part), is an annotated, chronological outline of references (abridged by the enormity of the World's documentation) regarding the background and the fight of the COVID-19 epidemic throughout U.S. Medicine and the United States public arena.[85,93] While much of the background information for this paper can be accessed through the Freedom of Information Act process, (1) a manuscript of this present completed article will be submitted in the future to the *New England Journal of Medicine* (NEJM)[98] for publication to specifically counter the paltering NEJM article: *Early Convalescent*

Plasma for High-Risk Outpatients with Covid-19 (and its supplement)[99,100]; (2) will also be submitted to the NIAID case #12276 file for historical preservation and availability to all wishing to request it and read it through the formal process under the Freedom of Information Act, 5 U.S.C. 552[95-97]; and to other Federal agencies, companies, individuals, etc. for whom this article will be instructive. I see this as my personal ethical duty to reconcile and correct the misinformation submitted to history to the veteran patients for whom I served for over a quarter of a century under the auspices of the Veterans Health Administration (VHA), the people of America, and to humanity for all time as I am a physician and surgeon, former Professor of Surgery, and former Federal physician.

II. The rationale and methods of addressing Electronic Overwriting:

A. Data bases and source material used in the preparation of this paper: **Attachment VIII**)

B. The analysis of public information obscured by electronic overwriting and URL changes **See that which follows in this Section II and subsequent Section III**

C. Avoiding the misinformation of obfuscating, lies of omission, and paltering: In the development of this analysis, an extensive collection of source materials from Medical publications, Federal and International data bases, and other media were reviewed, correlated, and filed.(**Attachments II and III**) In dealing with Federal documents of the VA, the NIH, the FDA, etc. fact checking of previous earlier versions of a document was many times difficult, if not impossible, if the URL of the previous or original document had been changed and/or the previous versions had been electronically overwritten. If the URL of the document was known and the ***Internet Archive*** [87-89] had sometime in the last quarter of a century digitized the document, then using the ***Wayback Machine***[89] (**the search engine of the *Internet Archive***) and the present URL, previous captured versions of the document with the same URL could be located to scrutinize what had been electronically overwritten.

While there are many official policies and protocols positively detailing the methodology of electronic overwriting for secure data destruction [101-102], such an extensive electronic overwriting process destroys the previous unique-specifics of the documentation and terminates the electronic paper-trail of document evolution. **This subliminal, ubiquitous methodology is utilized extensively by many in the Executive Branch of the U.S. Government at the present time.** ***In the preparation of this present analysis, electronic overwriting pervasively terminated the chronological history of a document's existence and was extremely detrimental to the development of this present analysis.*** Within the Executive Branch of the Federal Government, this pervasive, overutilized, abusive *status quo* process of electronic overwriting destroys the document's paper-trail of the previous history which clearly violates the foundational intent of the Sarbanes-Oxley Act of 2002, 18 U.S.C. §1512(c)(1).[103] Such electronic misdirection or outright destruction of information—I would allege--is a flagrant criminal violation of U.S. law as was confirmed recently in the opening sentence of *Fischer v. United States*[104,105] by the Supreme Court of the United States on June 28, 2024:

> The Sarbanes-Oxley Act of 2002 imposes criminal liability on anyone who corruptly "alters, destroys, mutilates, or conceals a record, document, or other object, or attempts to do so, with the intent to impair the object's integrity or availability for use in an official proceeding." 18 U.S.C. §1512(c)(1).

This pervasive process of electronic overwriting permeates the Executive Branch of the Federal Government at present time which I would allege is a blatant violation of 36 CFR § 1222.26.[106] For example, in the VA's Veterans Health Administration (VHA), there is a > 64-page document entitled Directive 6300(1), RECORDS MANAGEMENT[107], dated October 22, 2018—which ironically is overwritten with a red stamp of the transmittal sheet: AMENDED September 22, 2020 making the previous official document of October 22, 2018 non-discoverable even with the Wayback Machine as its URL is uploaded to one's computer as an individualized .pdf file. VHA Directive 6300(1) specifically outlines the process, organization, preservation, and archiving of all records in the VHA to be consistent with the National Archives directive[108]: Universal Electronic Records Management (ERM) Requirements (https://www.archives.gov/records-mgmt/policy/universalermrequirements#:~:text=The%20Universal%20ERM%20Requirements%20identify,use%20when%20developing%20system%20requirements). No where is the word "overwriting" ever mentioned, permitted, or proscribed; but there are admonishments for maintaining documents, promoting access, and a prohibition against deletion of records and documentation:

> **What are the general recordkeeping requirements for agencies?**
>
> (a) To ensure the adequate and proper documentation of agency programs, each program must develop recordkeeping requirements that identify:
> (1) The record series and systems that must be created and maintained to document program policies, procedures, functions, activities, and transactions;
> (2) The office responsible for maintaining the record copies of those series and systems, and the applicable system administrator responsible for ensuring authenticity, protection, and ready retrieval of electronic records;
> (3) Related records series and systems;
> (4) The relationship between paper and electronic files in the same series; and
> (5) Policies, procedures, and strategies for ensuring that records and retained long enough to meet programmatic, administrative, fiscal, legal, and historical needs as authorized in a NARA-approved disposition schedule.
> (b) Agencies must capture, manage, and preserve electronic records with appropriate metadata and must be able to access and retrieve electronic records, including electronic messages, through electronic searches.
>
> 36 CFR 1222.26

One blatant example of a violation of intent of 36 CFR 1222.26 within the VHA is the past eleven-year history of VHA Directive 1063, UTILIZATION OF PHYSICIAN ASSISTANTS (PA), December 24, 2013.[109] The initial URL document **declared the VHA preemptive over all State Medical Boards** base on the Constitution of the United States of America. Consistent with the fact that there does not exist any nationwide physician assistant (PA) licensing board (there are no nationwide physician nor national nursing licensing boards), all state medical boards credential all physician assistants (PAs) explicitly mandating that all PAs are working under a scope of practice of a licensed physician and are not independent practitioners which was controverted in the original version of VHA Directive 1063 of December 24, 2013[109]:

> **2. BACKGROUND: …**
>
> c. Under the Supremacy Clause of the U.S. Constitution, States are prohibited from regulating or controlling the activities of the Federal Government without written Congressional consent; where Federal and State laws conflict, Federal law governs official actions of Federal employees. Examples of the types of activities that the Federal Government may establish are qualifications for employment and scopes of practice. Therefore, the establishment of scopes of practice for VA PAs defined by this Directive is without regard to State Practice Acts.

Today, when direct access is attempted employing the original URL of VHA Directive 1063 of December 24, 2013[110]: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958, one is electronically diverted to a download on one's computer only that is a .pdf file stamped AMENDED June 24, 2024: i.e., file:///Users/andrusmd1/Downloads/1063(2)_D_2013-12-24%20(21).pdf thus preventing the access of the original version of VHA Directive 1063 of December 24, 2013.[109]

> On August 14, 2014, an electronic copy of VHA Directive 1063 was initially captured by the *Internet Archive* of the original version of December 24, 2013--8 months after VHA Directive 1063 was originally published (uploaded to the *Internet*)[109]:
> https://web.archive.org/web/20140814150238/https:/www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958
>
> The May 17, 2022 version of VHA Directive 1063 which rescinded the misinterpretation / misapplication of the Supremacy Clause of the U.S. Constitution was captured by the *Internet Archive* on August 12, 2022, which was 3 months after the publication of the overwritten "AMENDED" VHA Directive 1063 of May 17, 2022 version and nine years and eight months from the publication of the original version of VHA Directive 1063[111]:
> https://web.archive.org/web/20220812082647/https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958
>
> The latest version of June 18, 2024, was captured by the *Internet Archive* on July 18, 2024, which was one month after the publication in the June 18, 2024 version and eleven years and seven months from the publication of the original version of VHA Directive 1063 which contained the misinterpretation /misapplication of the Supremacy Clause of the U.S. Constitution.[110]
> https://web.archive.org/web/20240718213316/https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958

Besides perpetuating electronic overwriting of a previous misinterpretation/misapplication of a foundational statement of the U.S. Constitution, the adjustments to this document over the last 11 years are clear violations of the Sarbanes-Oxley Act of 2002[103] and also violated the VHA and the U.S. National Archives directives for amending and preserving the historical paper trail. Both "AMENDED" versions of May 17, 2022, and June 18, 2024, retained in all three versions of VHA Directive 1063 Transmittal Sheets the responsible, "signatory" party for VHA Directive 1063 as listed: VHA Under Secretary for Health, Robert A. Petzel, M.D. Dr. Petzel resigned "under fire" over the Phoenix, Arizonia VA scandal, in May 2014—six months after the original VHA Directive 1063 was signed officially by himself.[112-113] Eight and ten years respectively, the "AMEMDED" VHA Directives 1063 versions have covered-up the misinterpretation / misapplication (which violates States rights) of the Federal Government Supremacy Clause under the U.S. Constitution of the United States of America,

> Please note, the VHA Under Secretary for Health, is the highest ranking Medical Officer in the U.S. Department of Veterans Affairs and leads the Veterans Health Administration (VHA). The VHA Under Secretary for Health oversees the 172 VA Medical Centers, >1300 CBOCs, and the VHA's part of the U.S. Department of Veteran Affairs' VA annual budget of over $300 billion.[114] Dr. Petzel[92,112-118], along with the other four of us, Andrus [37,83-85,90,92-94,140,249], Bowen[92], Garthwaite[92,119], and Roswell[92,120,121], was interviewed for the VHA Under Secretary for Health on December 10, 1999, by the VHA USH Commission with three of the individuals: Drs. Garthwaite, Petzel, and Roswell being subsequently referred for vetting to *The White House* in early 2000. Although at that specific moment in history, Dr. Garthwaite's name was submitted to the Senate and he was confirmed in the Spring of 2000, Garthwaite (2000 – 2002), Roswell (2002-2004), and Petzel (2010-2014) would serve as VHA Under Secretaries for Health.

Thus, using the *Internet Archive's Wayback Machine*[88,89] became the one most important fact-checking methodology employed extensively in the development of this paper providing a "following of the paper-trail" back to the origins of the documents regarding fundamental issues of the DHHS, the FDA, the NIH, the NIAID, the VHA, etc.

III. Fact checking and identifying misstatements, misinterpretations, and misrepresentations of official definitions result in *paltering* defilements, violations of Federal law, and lies of commission and omission (Attachments: III, VI, and **VIII, References of Attachments I-VIII).** As with electronic overwriting and URL obliteration, obfuscation of definitions is ethically wrong and led frequently to inappropriate or fallacious analyses, spurious conclusions, and incorrect policies and directives in U.S. Medicine's addressing of the America's COVID-19 epidemic. Ferreting out and defusing euphemisms[15] became another keystone, focused methodology of this research:

> The comedian George Carlin grounded his professional career in his satirizing our county's fixation on euphemisms.[15] In American society today, we seemingly have become unwittingly partners and victims to our willingness to euphemistically diminish our assessments to mediocrity--all too often, relegating the rejection of advancements of foundational concepts in Medicine to that of *Chronic Denial*. (**Attachment V**)[122-124] Throughout our society today, we have become comfortable with incorrectly expressing and flippantly misusing the definitions and meanings of words and phrases; ignoring essentials to the point of violating the intent of the rules of science, nature, and the laws of our country in our daily lives; lying sometimes by commission but, most of the time, by omission and paltering; and championing *ad nauseam* the *ad hominem* attacks levelled against our fellow man as a standard methodology of bravado and self-assertiveness to discard the worth of our fellowman. During the COVID-19 epidemic, we, as individuals, in the United States of America through our institutions like that of Academic Medicine, Medical Publications, the U.S. Federal Government, etc. have distorted foundational concepts in Medicine which have resulted in disastrous outcomes for individuals, families, and communities throughout our country which were concomitant with >1,000,000 deaths associated with the American COVID-19 epidemic.

Much of our short-comings during the United States COVID-19 epidemic were ambiguous definitions, misinterpretation of definitions, and resultant obfuscations (***Palterings***) due to:

1. our naïve, pervasive utilization of euphemisms and manipulation of definitions
2. employment of electronic overwriting of policies, directives, and other documents with resultant subliminal electronic destruction of previous versions;
3. disregard for human rights by *de facto* suspension of EMTALA and desuetude of the Right to Try Act, etc.;
4. disregard for and misapplications of standardized definitions and policies of the FDA, the NIH, the CDC, the VA, and Medicine-in-general;
5. emphasis on our country's obsession that money can buy the right thing in Medicine which is far-from-the-truth;
6. disregard and daily misapplication to the truism that "…You cannot legislate for virtue"; and
7. unrestrained lies of commission and omission that indirectly resulted in greater than 1,000,000 deaths associated with these individuals' contraction of the coronavirus, SARS-CoV-2, (COVID-19).

Most importantly in the methodology of addressing of definition ambiguity, misinterpretation, misapplication, and paltering, the first part of the Results portion of this paper is a succinct outline: Table 1: Digital vs. Analog—Yes, No, Maybe in Medicine and Treatment of Covid-19. Table 1 is probably the most of important foundational methodology within this paper in the analyzing of branchpoint definitions with regards to the misapplications of definitions within Medicine, Medical Statistics[Attachment VI], and the Legal Mandates[2.2 Definition_Fundamentals_Legal_Mandates background] involving specifically the U.S.A.'s response to the coronavirus, SARS-CoV-2, COVID-19. In **Table 1**[2.1 Table 1- Digital vs. Analog-Yes, No, Maybe in Medicine and Treatment of Covid-19], there is a categorizing of branchpoints as Positive, Relative, and Negative. In Medicine, as in life, there is only one absolute branch point: **Lived** versus **Died**. In our present computerized mindset of a "binary look" at the World today, we have mistakenly equated all decisions to Yes versus No equaling the digitalization of 1 versus O, e.g.: Lived versus Died, etc. The World and Medicine overwhelmingly are of the Relative or Analog –not just Yes/No. **Table 1** is a hierarchical analysis that was then employed in the development of the **Results, Discussion, and Recommendations** portions of this paper. This analysis is based on the communications from April 5, 2020, going forward from Dr. Andrus to the National Institute for Allergy and Infectious Diseases (NIAID), Case file #12276; the FDA; the VA; *The White House*, etc. and the summary publication: Andrus CH: *Dear Mr. President: COVID-19 and Where We Went Wrong* of February 2, 2023, uploaded to the *Internet Archive* on 2023-09-12 https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02 [37, 83-85,90,92,93]

IV. Pathophysiology, Statistics, Legal Abridgments: Some of the aberrancies in our applications of foundational principles and tenets of Medicine and, I allege, the violations of legal mandates throughout the last five years resulted from the repeated euphemistic manipulations of definitions[15], electronic overwriting, destruction-of-access-to-a-logical-pathway by changing electronically the ULS addresses, etc.[Attachments VIII] Some of the analyses have been incorporated into the **Discussion** section of this paper and referenced to provide the reader the opportunity to explore these inconsistencies in more depth.

Unfortunately, all this information has been tainted with the euphemistic manipulation of definitions, the mistaken emphasis on self-serving theories, and the deemphasis of the clarity and importance of the pathophysiology of the disease cause by coronavirus, SARS-CoV-2, COVID-19. **The resultant logic of direct treatment (not prophylaxis) based on the clinical expression of the pathophysiology of COVID-19 with immunotherapy, antivirals, etc. has been dismissed for all intensive purposes by the NIH and FDA.** Thus, the most important essence of this present paper's methodology is to provide the reader with reference foundational terminology and applications to organize pertinent facts from self-serving fiction. **Attachment III: *Reductio ad Absurdum:* The COVID-19 Tale of Two Presidents, the Ramifications of Fifty Years of American Scandal, Therapeutic Nihilism, and Medical Stupidity**[0.4 Attachment III Reductio ad Absurdum] is the face sheet of a 100-page document (between pages e31 to e130) summarizing that which was submitted to President Biden over the course of his term-in-office.[94,123] The complete 848 page summary of submissions to the FDA, the NIAID, the VA, and *The White House* under NIAID case file #12276 was uploaded to the *Internet Archive*

entitled: ***Book 4:*** *President Biden's July 7, 2023 Response Letter to Dr. Andrus' submission of 2023-04-27 update 11-7-23.pdf*[93] :

> ***Book 4:*** *President Biden's July 7, 2023 Response Letter to Dr. Andrus' submission of 2023-04-27 update 11-7-23.pdf* Internet Archive, Uploaded 2024 Feb 05, https://archive.org/details/book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong/ , **[Only 382 pages sometimes can be accessed, thus it was again uploaded on March 5, 2024, to the *Internet Archive* as Title: *0.4 Book 4 Biden response to the Summary of Book 1 COVID 19 And Where We Went Wrong 2nd Attemp*** https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp *** NIH NIAID Case #12276

In the following Results section, the treatment with immunoglobulins of a viral infection with immunoglobulins and an outline of pertinent definitions in Table 1[2.1 Table 1 Digital v. Analog—Yes, No, Mavbe in Medicine and Treatment of Covid-19] are discussed. Then, using comparison statistics, e.g.: 2x2 contingency tables, a series of Chi Square analyses are correctly applied to contradict the invalid impression expressed throughout the literature regarding the efficacy of COVID-19 Convalescent Plasma and implemented by U.S. Medicine. 2x2 contingency tables of the FDA's published conclusions of August and September 2020 were reconstructed from the published FDA conclusions by a series of iterative Chi Square analyses using the statistical program: GraphPad Prism 10[125] (and SAS's StatView II[126] was used throughout the five years in other analyses).

Results:

All of us, as physicians, should have the fundamental knowledge regarding early treatment (≤72 hours from diagnosis) of a novel virus with antivirals [16,37,128-130,145,148-157,186,196,202-206] and synergistically[129,196,202-204] with exogenous immunoglobulins.[127-130] (An important, universal, concept of the time-dependent effect of *Passive Immunization* on the initial viremia and the later host-systemic phase applicable to COVID-19 and all viruses is depicted in the self-explanatory Figure 8.2 of Chapter 8: *Passive Immunization* by Slifka MK, Amanna IJ: Chapter 8: Passive Immunization. Plotkin's Vaccines 7th Ed, 2018: p 8,epage 6.[34]) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151993/pdf/main.pdf. **During the COVID-19 Pandemic, through the truly altruistic, selfless disclaimer of the publisher, *ELSEVIER*, Figure 8.2 that follows was made available to the World** *(and unfortunately, we did not pay attention and emphasize Figure 8.2's importance):*

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

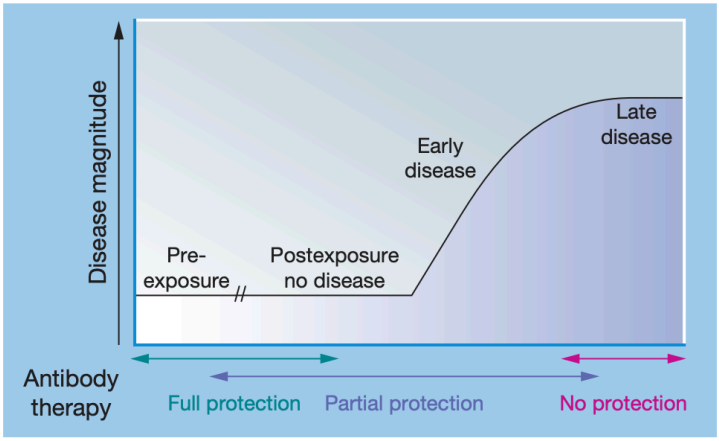


Figure 8.2. Efficacy of passive immunity decreases with disease progression. Full protection from symptomatic disease is best achieved through prophylactic administration of antibody therapy prior to exposure or infection. However, antibody therapy may also be highly effective at early points postexposure, prior to the onset of disease symptoms. Passive immunity is generally less effective when administered after the onset of symptomatic disease, and typically shows little to no clinical benefit once severe late-stage disease has occurred.

Overall, U.S. Medicine during the COVID-19 epidemic response was typified by: (1) a chronology of errors, political misinformation, and self-centered promotion and advancement;

(2) disregard for some foundational concepts of medicine in the treatment (not prophylaxis) of viruses; and (3) a morass of self-serving ignorance, arrogance, and stupidity contributory to our minimizing the importance for the immediate TREATMENT with immunoglobulins and antivirals of **ALL INFECTED INDIVIDUALS** early in the course (<72-96 hours from diagnosis) of their individually-contracted disease which have been foundational pillars of therapeutics for novel viruses throughout the twentieth century. While we officially hailed **prophylaxis** (Active Immunization/Vaccines) as the foremost management methodology during the American COVID-19 epidemic of the World-wide pandemic, we, as U.S. Medicine, ***FAILED to treat*** *immediately (within 72-96 hours of diagnosis) all those infected* with the novel virus: coronavirus, SARS-CoV-2, COVID-19 with immunoglobulins and antivirals!

On March 2, 2021, this misdirected obfuscative paltering in U.S. Medicine culminated in the FDA rejecting immediate treatment with COVID-19 Convalescent Plasma (CCP) presenting to emergency departments.[131] This resulted in a nationwide restriction in use or complete discontinuation of blood bank collections, processing, and distribution of COVID-19 Convalescent Plasma.[132-134] The *ex post facto* publication of the results of the NIH funded SIREN-C3PO trial[131-138] in a November 2021 article in the *New England Journal of Medicine*[99,100]: (1) violated the basic tenets of medical statistics, our ethical responsibility to educate truthfully, and our human sensibilities and responsibilities of equitable, compassionate care towards all our fellow Americans:

> Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, McDyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLW, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit R, Barsan W, and Callaway CW for the SIREN-CEPO Investigators: **Early convalescent plasma for high-risk outpatients with Covid-19**. N Engl J Med 2021 November 18; 385 (21): 1951-1960. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784 [99]
>
> Korley FK, Durkalski-Mauldin V, Yeatts SD, *et.al.*: **SUPPLEMENTARY MATERIAL to Early convalescent plasma for high-risk outpatients with Covid-19.** N Engl J Med 2021 November 18; 385 (21): 1951-1960 can be found online at the bottom of the page of the online version of this article: https://www.nejm.org/doi/full/10.1056/NEJMoa2103784#ap0 [100]

and (2) this NEJM article inappropriately and disingenuously validated the NIH funded SIREN-C3PO Randomized Controlled Trial (RCT) trial as an appropriate multi-institutional RCT.[135] If the SIREN-C3PO RCT protocol was reviewed reasonably by any non-proprietary University-based IRB, it would have been rejected as extremely underpowered.[99,139,140]

In March 2021, in acting upon the unpublished "results" of the SIREN-C3PO Clinical trial.gov NCT04355767 [131], that later would be published in the *New England Journal of Medicine* (NEJM), November 18, 2021: Early Convalescent Plasma for High-Risk Outpatients with Covid-19[99,100], the NIH, the FDA, and U.S. Medicine in general was misled into condoning the driving of the *final nail-in-the-coffin* to the appropriate use of ***Passive Immunization*** for ALL in an organized, systematic administration early (<72 – 96 hours from diagnosis) during the course of the disease. In the Spring and Summer of 2021, the American blood banks[132-134] acted upon the unpublished SIREN-C3PO clinical trial even though the actual "results" were not presented / published to U.S. Medicine and the American public until 8 months later.[99-100] Thus, *The New England Journal of Medicine* permitted publication of the article epitomizing a travesty of lying

with statistics entitled: Early Convalescent Plasma for High-Risk Outpatients with Covid-19[99]: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784 and its Supplement Appendix[100] accessible only through the NEJM's on-line URL site: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf through clicking are the box at the end of the website leading to the URL: https://www.nejm.org/doi/full/10.1056/NEJMoa2103784 . In so doing, the NEJM abandoned its promise to humanity to uphold the tenets that the NEJM professes to the World as it is a signatory and has ongoing participating committee members to the International Committee of Medical Journal Editors (ICMJE). The NEJM has failed to live up to that which it boasts: "The most trusted, influential source of new medical knowledge and clinical best practices in the world"[75-80,141-143]:

> **Integrity Safeguards**[80]
>
> The *New England Journal of Medicine (NEJM)* is committed to publishing the highest quality research and reliable, authoritative review articles. No NEJM editor is permitted to have any financial relationship with any biomedical company. NEJM strives to identify, vet, and publish research that will make a difference in medicine. The mainstays of credibility are:
>
> - Editorial independence
> - Academic rigor in editing and reviewing research
>
> NEJM has taken a notable leadership role over the past decade and a half in advocating for stronger, more consistent standards of integrity across the entire medical publishing industry. For example, NEJM:
>
> - Played a significant role in the 2005 campaign to require clinical trial registration.
> - Since 1984, has requested author disclosures, and pioneered in 2009 with the International Committee of Medical Journal Editors (ICMJE), a universal disclosure form that requests that authors report all relevant financial conflicts during the 36 months before publication.
> - Took the lead among medical journals in 2011 to publish study protocols with all randomized, controlled trials. NEJM is still one of the few general medical journals that publishes protocols with all randomized trials.
> - Broke new ground, along with the ICMJE, in requiring sharing of clinical trial data. As of 2018, NEJM required authors to include a data sharing statement when submitting an article for publication. In 2019, they were required to enter a data sharing plan in the trial's registration.
>
> Beyond promoting clinical trial registration and ICMJE universal standard disclosure for all scientific medical reporting, NEJM:
>
> - Works diligently to ensure that research conclusions are neither overstated nor misleading, that results are placed in proper context for clinical practice, and that peer review editorial informs editorial decision.
> - Grants immediate free access to low-income countries through partnership with Reasrch4Life's Access to Research in Health (Hinari) program.
> - Enforces strict rule around disclosure of paper authorship.
> - Carefully reviews manuscript, protocol, and trial registrations of every randomized clinical trial.
> - Maintains strict separation between editorial and business considerations.

Early Convalescent Plasma for High-Risk Outpatients with Covid-19 palteristically concluded in its abstract's conclusion:

> The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression. (SIREN-C3PO ClinicTrials.gov number, NCT04355767).[99]

Contrary to the above statement, a 2x2 contingency table and Chi-square analysis using GraphPad Prism 10 for MacOS[125] of the hierarchal figure on page 1955 of the November 18, 2021, NEJM article[99], entitled: Figure 1. Enrollment, Randomization, and Analysis Populations., yields an outcome that <u>is not</u> (statistically) significant: **Table 2: Chi-square analysis of Figure 1 of NEJM article, November 18, 2021:**

Contingency — NEJM Paper Figure 1

Table Analyzed	Data 1		
P value and statistical significance			
Test	Fisher's exact test		
P value	0.1224		
P value summary	ns		
One- or two-sided	Two-sided		
Statistically significant (P < 0.05)?	No		
Data analyzed	**Lived**	**Died**	**Total**
CCP	243	5	248
Placebo	248	1	249
Total	491	6	497
Percentage of row total	**Lived**	**Died**	
CCP	97.98%	2.02%	
Placebo	99.60%	0.40%	
Percentage of column total	**Lived**	**Died**	
CCP	49.49%	83.33%	
Placebo	50.51%	16.67%	
Percentage of grand total	**Lived**	**Died**	
CCP	48.89%	1.01%	
Placebo	49.90%	0.20%	

In fact, while there were five deaths in the CCP group (experimental group) and only 1 in the control (placebo) group, these were not (statistically) significant. The real reason these results for "death" were not significant is that these reported SIREN-C3PO results made the assumption that this subgroup of 497 patients only: CCP: 243 lived v 5 died versus the placebo control of 248 lived v 1 died, **was representative** of the <u>all-inclusive U.S. population presenting to ERs with COVID-19 symptomatology equal to or over the age of 50 years</u>**—WHICH IS NOT VALID**. This study was markedly, inherently skewed as non-representative of the proposed-to-be-studied U.S. population from the onset due to a multitude of factors of which the most prominent is that the study reported an exclusion of 3479 of 3990 (87.2%) from inclusion group in the randomization process. This initial assessment of the eligibility process was markedly not representative of the U.S. population acutely infected with coronavirus, SARS-CoV-2, COVID-19, as was purported to be the essence of the Methods section of the Abstract of <u>Early Convalescent Plasma for High-Risk Outpatients with Covid-19</u>[99]:

> METHODS
> In this randomized, multicenter, single-blind trial, we assigned patients who were being treated in an emergency department for Covid-19 symptoms to receive either one unit of convalescent plasma with a high titer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or placebo. All the patients were either 50 years of age or older or had one or more risk factors for disease progression. In addition, all the patients presented to the emergency department within 7 days after symptom onset and were in stable condition for outpatient management. The primary outcome was disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization. Secondary outcomes included the worst severity of illness on a 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause.

Thus, most-importantly, the primary, subliminal null hypothesis (H_0) was not supported in the underlying intent, process, and publication of the paper: The mortality outcome of those included versus those excluded must be consistent with the historical population matched controls (Graphs IV above):

Table 3: Chi-square Analysis using GraphPad Prism 10 of NEJM Article's Non-Representation of the U.S. Population by Age-adjusted Mortality

Contingency	Chi-square Included v Excluded-	Lived v Died for ≥ 50 yr old	
Table Analyzed	Data 1		
P value and statistical significance			
Test	Fisher's exact test		
P value	<0.0001		
P value summary	****		
One- or two-sided	Two-sided		
Statistically significant (P < 0.05)?	Yes		
Data analyzed	**Lived**	**Died**	**Total**
Included	491	6	497
Excluded	3041	452	3493
Total	3532	458	3990
Percentage of row total	**Lived**	**Died**	
Included	98.79%	1.21%	
Excluded	87.06%	12.94%	
Percentage of column total	**Lived**	**Died**	
Included	13.90%	1.31%	
Excluded	86.10%	98.69%	
Percentage of grand total	**Lived**	**Died**	
Included	12.31%	0.15%	
Excluded	76.22%	11.33%	

Contingency	Chi-square Included v Excluded-	Lived v Died for mean 60 yr old	
Table Analyzed	Data 3		
P value and statistical significance			
Test	Fisher's exact test		
P value	<0.0001		
P value summary	****		
One- or two-sided	Two-sided		
Statistically significant (P < 0.05)?	Yes		
Data analyzed	**Lived**	**Died**	**Total**
Included	491	6	497
Excluded	2659	634	3293
Total	3150	640	3790
Percentage of row total	**Lived**	**Died**	
Included	98.79%	1.21%	
Excluded	80.75%	19.25%	
Percentage of column total	**Lived**	**Died**	
Included	15.59%	0.94%	
Excluded	84.41%	99.06%	
Percentage of grand total	**Lived**	**Died**	
Included	12.96%	0.16%	
Excluded	70.16%	16.73%	

Contingency	Chi-square Included v Excluded-	Lived v Died for mean 70 yr old	
Table Analyzed	Data 4		
P value and statistical significance			
Test	Fisher's exact test		
P value	<0.0001		
P value summary	****		
One- or two-sided	Two-sided		
Statistically significant (P < 0.05)?	Yes		
Data analyzed	**Lived**	**Died**	**Total**
Included	491	6	497
Excluded	2677	816	3493
Total	3168	822	3990
Percentage of row total	**Lived**	**Died**	
Included	98.79%	1.21%	
Excluded	76.64%	23.36%	
Percentage of column total	**Lived**	**Died**	
Included	15.50%	0.73%	
Excluded	84.50%	99.27%	
Percentage of grand total	**Lived**	**Died**	
Included	12.31%	0.15%	
Excluded	67.09%	20.45%	

Contingency	Chi-square Included v Excluded-	Lived v Died for mean 80 yr old	
Table Analyzed	Data 5		
P value and statistical significance			
Test	Fisher's exact test		
P value	<0.0001		
P value summary	****		
One- or two-sided	Two-sided		
Statistically significant (P < 0.05)?	Yes		
Data analyzed	**Lived**	**Died**	**Total**
Included	491	6	497
Excluded	2496	997	3493
Total	2987	1003	3990
Percentage of row total	**Lived**	**Died**	
Included	98.79%	1.21%	
Excluded	71.46%	28.54%	
Percentage of column total	**Lived**	**Died**	
Included	16.44%	0.60%	
Excluded	83.56%	99.40%	
Percentage of grand total	**Lived**	**Died**	
Included	12.31%	0.15%	
Excluded	62.56%	24.99%	

Figure 1, page 1955[99] of:

> Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, McDyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLW, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit R, Barsan W, and Callaway CW for the SIREN-CEPO Investigators: **Early convalescent plasma for high-risk outpatients with Covid-19**. N Engl J Med 2021 November 18; 385 (21): 1951-1960. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784 [99]
>
> (--also inclusive is the NEJM supplement:
> Korley FK, Durkalski-Mauldin V, Yeatts SD, *et.al.*: **SUPPLEMENTARY MATERIAL to Early convalescent plasma for high-risk outpatients with Covid-19.** N Engl J Med 2021 November 18; 385 (21): 1951-1960 can be found online at the bottom of the page of the online version of this article: https://www.nejm.org/doi/full/10.1056/NEJMoa2103784#ap0 [100])

is a hierarchical algorithm which biased internally the SIREN-C3PO RCT by eliminating the vast majority of the patients presenting with "early" COVID-19 as the inclusion criteria was regulated to a randomization of the administration of CCP versus placebo based on an arbitrary, nebulous, individual qualitative parameter: "…high-risk outpatients with Covid-19"[99] excluding

those qualitatively designated as well-enough to be discharged without treatment or too sick requiring hospitalization, e.g.:

a. a majority of those presenting to the Emergency Rooms in this multi-institutional RCT were excluded: **3479/3990 = 87.2% excluded**;

b. the inexactitude of the ***variable qualitative nature*** of the exclusion criteria at both extremes (tails of the bell-shaped curve) of a normal population distribution curve is non-sensical skewing of the analysis and making any conclusions impossible, e.g. 1). where the patients were not sick enough for inclusion ["had no trial defined Covid-19 risk factor" (682) or "had no Covid-19 symptoms" (153) = **835 or 24.0% of those excluded**]; 2.) where the patients were too sick for inclusion ["symptoms >7 days" (955) or "were no longer intended for discharge" (271) = **1226 or 35.2% of those excluded**]; or 3.) where patient's presentation was not convenient for the institution for inclusion in the RCT ["had ED visit outside of screening hours" (561), "were missed during the screening hours" (39), or "had site operational issue" (110) = **710 or 20.4% of those excluded**]-- a total exclusion number due to the inexactitude of the ***variable qualitative nature*** of the exclusion criteriae was (835 + 1226 + 710)/ 3479 = **(2771/ 3479) = 79.6% of those excluded**;

c. inclusion of 30 of the 38 institutional sites (80%) which individually contributed a limited, insignificant number of patients to the randomization process is disingenuous at best. The distribution of contributing institutions can be found in the online Supplementary Appendix (page 2-5)[100] **ONLY** which defies a controlled randomization in the total trial by relegating it at the local institutional level. Within the individual contributory institutions, their numbers are statistically insignificant, e.g.: How does one randomize 1 patient between the CCP group vs. the control group in the 4 institutions that contributed only 1 patient each?— You can't split a patient in half to randomize from one institution with only one submission!

   i. Above 20 subjects from eight institutions (which should be statistically valid for analysis):
   50,43,33,27,26,25,24,23 = **251 inclusive subjects from 8 institutions:**
   [251/(251+246)] x100 = **50.5% subjects included in the final analysis from institutions submitting more than 20 subjects per institution**

   ii. Below 20 subjects per institution (which are considered statistically insufficient per each individual participating institution) from the 38 participating institutions:
   18 subjects from 3 institutions (45)
   12 subjects from 2 institutions (24)
   11 subjects from 2 institutions (22)
   10 subjects from 2 institutions (20)
   9 subjects from 3 institutions (27)
   8 subjects from 3 institutions (24)
   7 subjects from 2 institutions (14)
   6 subjects from 3 institutions (18)

5 subjects from 1 institution (5)
4 subjects from 6 institutions. (24)
3 subjects from 5 institutions (15)
2 subjects from 2 institutions. (4)
1 subject from 4 institutions (4)
246 inclusive subjects from 38 institutions submitting less than 20 subjects per institution [246/(251+246)] x 100 = **49.5%**]

{Please note from Figure 1 on page 1955 of the NEJM article, the total of 497 included are consistent with the final number assigned to receive convalescent plasma ["246 were included in intention-to-treat analysis"] and ["254 were included in intention-to-treat analysis]}

d. corroborated the NIH's discontinuation of the SIREN-C3PO trial which led to the official disappearance of the collection, processing, and distribution by the United States blood banks of CCP in the spring of 2021 for early treatment of individuals acutely infected with COVID-19 with COVID-19 Convalescent Plasma[131-134];

e. and legitimated before the American public greater than 384,000 deaths involving COVID-19 in 2020 (prior to the vaccines) of unvaccinated / immune naïve individuals in which the vast majority could have been treated within 72-96 hours of diagnosis with immunoglobulin therapy (CCP or monoclonal antibodies) and the antiviral remdesivir [148-157] which was *de facto* tantamount to the DENIAL of their individual patient rights guaranteed under EMTALA[158-161] and/or the Right to Try Act of 2018.[162-165]

Throughout the RESULTS and DISCUSSIONS of this paper, it will be demonstrated that the FDA calculations and presentations[166-167] before the American people in August and September 2020, correctly and positively confirmed COVID-19 Convalescent Plasma's safety and efficacy using the outcomes data of the Mayo Clinic / FDA Expand Access (Compassionate Use) Protocol (EAP) under the direction of the Principal Investigator, Michael Joyner, M.D., Ph.D.[168-180] Despite the fact that "from April 3 to August 23, 2020, 105,717 hospitalized patients with severe or life-threatening COVID-19[178] were enrolled in the EAP"[181,182], it was consistently demonstrated (1) that there was safety in the administration of CCP and (2) there was a survival advantage if the CCP was administered to COVID-19 infected individuals within the first 72 hours after diagnosis with high titer CCP. **Prior to the blood banks[132-134] in America in the Spring 2021 discontinuing collection of COVID-19 Convalescent Plasma (CCP) for processing, distribution, and administration and thus *de facto* bureaucratically discontinuing general availability within the United States going forward *ad infinitum*, the FDA in February 2021, correctly concluded that there is a survival advantage with CCP treatment--early after diagnosis--of high-dose CCP versus withholding CCP for all non-vaccinated and/or COVID-19-immune-naïve acutely COVID-19-infected individuals:**[181,182]

> **Recommendation:** The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment hospitalized patients with COVID-19 early in the course of hospitalization. The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be

> evaluated to further characterize the patient populations and product characteristics meeting EUA criteria. (2| Page)

The FDA announcement[166] of August 23rd 2020, based on the Mayo /FDA Clinic CCP protocol, presented in a Presidential news conference[164] on the eve of the Republican National Convention **failed**: (1) to define the attributes and positive outcomes of COVID-19 Convalescent Plasma (CCP) to the scientific community and the American public, (2) *de facto* interrupted the availability of CCP through the Mayo Clinic / FDA Convalescent Plasma Protocol (Mayo/FDA) by compelling the discontinuation of the Mayo/FDA protocol, and (3) was dismissed by the scientific community. Former FDA Commissioner, Stephen Hahn, M.D., has been blamed[183] probably unfairly, regarding this debacle:

> The push to get a vaccine approved before the election on November 3 grew stronger and stronger. The FDA commissioner, Stephen Hahn, an oncologist from MD Anderson Cancer Center in Houston, Texas, had made some missteps early in his tenure. Given the White House push for hydroxychloroquine, he had agreed to its emergency authorization, which ultimately back. Next, in a press conference about the efficacy of convalescent serum he got the percent of improvement wrong, later apologizing for mistakenly exaggerating the data. After these incidents, he made it clear to the Trump administration that in terms of vaccine authorization he and his agency would not be pressured into taking scientifically incorrect action; that vaccine approvals would not be rushed just because the White House hoped that they would be approved before the election. Rather, the FDA would follow all proper procedures to make sure they were safe and effective. Steve and the FDA did their jobs well regarding decisions about the COVID vaccines.

Even though the reported results on that day are a gross averaging of the mortality and the prevention of mortality (survival) by the administration of exogenous immunoglobulin (CCP), both in the reporting of mortality vs titers[166] (Graphs I) and in the reporting of mortality vs. ID50 (concentration of neutralizing antibodies), at the 7th day (Graphs II) and the 28th day (Graphs III) a month later before Congress on September 23, 2020[167], it can be graphically documented appropriately that the logarithmic plot of SURVIVAL (like a Michaelson-Menten plot[184,185]) was significantly (statistically) increasing with increasing neutralizing antibody titers (ID50) in individuals that were treated in <u>less than 72 hours during the viremic phase of Covid-19[186] (both all individuals and below age 80 years) from the initial diagnosis with COVID-19 convalescent plasma</u>. The survival results when plotted in a logarithmic fashion of percentage survival as Michaelson-Menten graphs that follow demonstrated increasing survival approaching an asymptotic maximum survival in the early-treated patients (<u>≤</u> 72 hours) when treated within the viremic phase[186] of the disease with increasing titers / ID50 concentrations of COVID-19 Convalescent Plasma.

By decade, the increased rate of mortality (increasing ~0.5% per-year-of-age over 49) calculated and graphed from mortality data publicized by the CDC[187] over the initial 17-months when the majority of deaths were in unvaccinated patients immunologically naïve to COVID-19 *against* increasing age (Graph IV) was consistently increasing with the coefficient of determination of the least-squared graphing, Graph IV, figure 2, calculated to be $r^2 = 0.9916$ for those greater than 49 years of age. Thus, Graph IV denote that all <u>randomized controlled trials</u> (RCT) performed during the American COVID-19 epidemic were ***UNPOWERED*** being spread over multiple decades of life with an increasing mortality of ~0.5% per-year-of age over 49. The results announced by the FDA on August 23, 2020[166], are thus muted due to inclusion of multiple decades but were still ***CORRECTLY*** reported by the FDA as a significant outcome ($p < 0.03$) in the <u>≤</u>72 hour, non-intubated, <u>≤</u> 80 yr group when a 2x2 Chi-square analysis was performed and

confirmed by this analysis (Graphs I) , i.e.: *CCP High dose* v. *CCP Low dose* crossed with *alive* v. *dead* at 7 days. It is extremely important to understand that in the FDA's analysis there were three critical clinical variables subliminally influencing the FDA's reports:

1. **Severity of Disease: Non-intubated:** means that on the average, these individuals were less severe in the viremic[186] (initial) phase of the disease (≤ 72 hours). Those undergoing treatment at >72 hours which is the phase of host response—the cytokine cascade and the bradykinin storm--the individual patient had progressed prior to administration of CCP to the full-blown COVID-19.[188-196] The subsequent severe host response to COVID-19 of the initiation of the cytokine cascade and the bradykinin storm[188-196] involves the interference of the renin-angiotensin system (RAS) as the coronavirus, SARS-CoV-2 entry into the pneumonocytes is associated with the ACE-2 receptor.

2. **Time: ≤72 hours:** means that on average each unique individual was in the viremic[186] (initial phase) of the COVID-19 infection with the coronavirus, SARS-CoV-2.

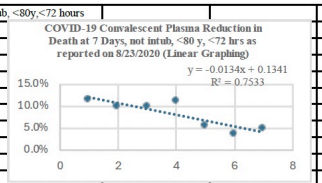
3. **Age:** was associated with death correlating with an increasing slope rate of ~0.5 % mortality by increasing year after age 49 (Graphs IV).[187] **What is not reported in the FDA's cursory report is a segmental analysis (e.g., by decades) correlated with survival**— (Unfortunately, this is speculatively, because the FDA probably could not report these as there were probably too-few patients (underpowered) to distribute in 2x2 contingency tables of some of the age-decade-dependent subgroups**.)** The Michaelson-Menten graphs of survival developed from that which was reported by the FDA are, in actuality, summations of a series of aged-dependent (e.g.: by decade of age) of Michaelson-Menten-like graphs. To be pathophysiologically-consistent, though, with large enough subgroups numbers (n), these subgraphs should demonstrate a series of age/decade-associated parallel logarithmic survival curves for those *non-intubated* and having been given CCP within <72 hours of initial diagnosis dependent on the patient subgroup numbers that allow for an adequate power (Power = 1 - β) in the Chi-square analysis.

Graphs I: COVID-19 Convalescent Plasma (CCP) in Mortality (and Survival) at 7-days after treatment reported by the FDA on August 23, 2020, plotted against increasing titer concentrations.[166]

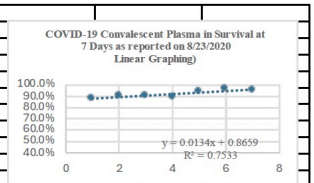
0.5 COVID-19 Convalescent Plasma Reduction in Death.xlsx

Table listing titers: at day 7, not intub, <80y,<72 hours

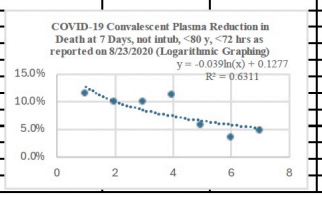
	Death
1=(<1:80)	11.5%
2=(1:80)	10.0%
3=(1:160)	9.9%
4=(1:320)	11.2%
5=(1:640)	5.6%
6=(1:1280)	3.5%
7=>=1:2560	4.8%



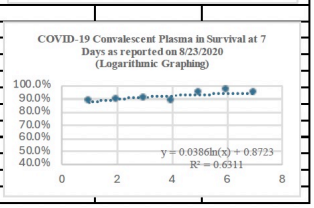
	Survival
1=(<1:80)	88.5%
2=(1:80)	90.0%
3=(1:160)	90.1%
4=(1:320)	88.8%
5=(1:640)	94.4%
6=(1:1280)	96.5%
7=>=1:2560	95.2%



	Death
1=(<1:80)	11.5%
2=(1:80)	10.0%
3=(1:160)	9.9%
4=(1:320)	11.2%
5=(1:640)	5.6%
6=(1:1280)	3.5%
7=>=1:2560	4.8%



	Survival
1=(<1:80)	88.5%
2=(1:80)	90.0%
3=(1:160)	90.1%
4=(1:320)	88.8%
5=(1:640)	94.4%
6=(1:1280)	96.5%
7=>=1:2560	95.2%

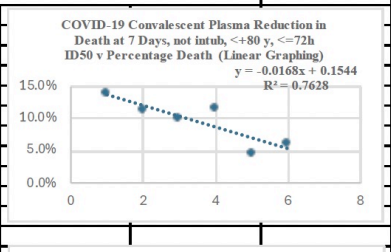


Graphs II: COVID-19 Convalescent Plasma (CCP) in Mortality (and Survival) at 7-days after treatment reported by the FDA in testimony before Congress on September 23, 2020, plotted against increasing ID50 of neutralizing antibody concentration ranges.[167]

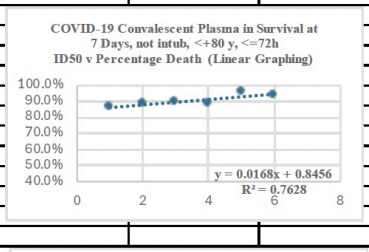
0.5 COVID-19 Convalescent Plasma Reduction in Death.xlsx

Not intub, <+80 y, <=72h Percentage Death in Hospitalized Patients by **Day 7**

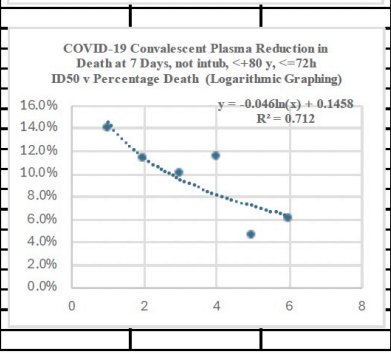
ID50	Death
1 = 0 - 62	14.0%
2 = 63 - 125	11.3%
3 =126 - 250	10.0%
4 =251 - 500	11.5%
5 =501 - 1000	4.5%
6 =1000+	6.0%


COVID-19 Convalescent Plasma Reduction in Death at 7 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Linear Graphing)
y = -0.0168x + 0.1544
R² = 0.7628

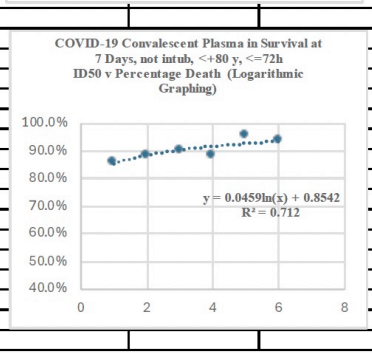
ID50	Survival
1 = 0 - 62	86.0%
2 = 63 - 125	88.7%
3 =126 - 250	90.0%
4 =251 - 500	88.5%
5 =501 - 1000	95.5%
6 =1000+	94.0%


COVID-19 Convalescent Plasma in Survival at 7 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Linear Graphing)
y = 0.0168x + 0.8456
R² = 0.7628

ID50	Death
1 = 0 - 62	14.0%
2 = 63 - 125	11.3%
3 =126 - 250	10.0%
4 =251 - 500	11.5%
5 =501 - 1000	4.5%
6 =1000+	6.0%


COVID-19 Convalescent Plasma Reduction in Death at 7 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Logarithmic Graphing)
y = -0.046ln(x) + 0.1458
R² = 0.712

ID50	Survival
1 = 0 - 62	86.0%
2 = 63 - 125	88.7%
3 =126 - 250	90.0%
4 =251 - 500	88.5%
5 =501 - 1000	95.5%
6 =1000+	94.0%

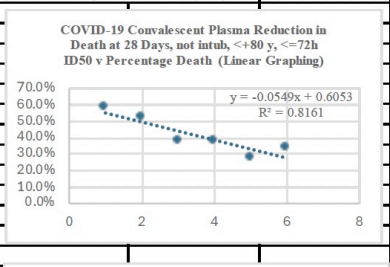

COVID-19 Convalescent Plasma in Survival at 7 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Logarithmic Graphing)
y = 0.0459ln(x) + 0.8542
R² = 0.712

Graphs III: COVID-19 Convalescent Plasma (CCP) in Mortality (and Survival) at 28-days after treatment reported by the FDA in testimony before Congress on September 23, 2020, plotted against increasing ID50 of neutralizing antibody concentration ranges.[167]

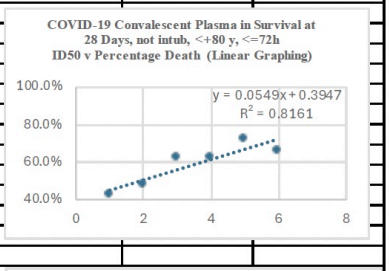
0.5 COVID-19 Convalescent Plasma Reduction in Death.xlsx

Not intub, <+80 y, <=72h Percentage Death in Hospitalized Patients by **Day 28**

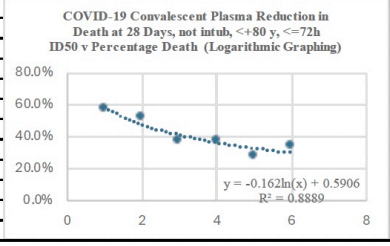
ID50	Death
1 = 0 - 62	58.0%
2 = 63 - 125	52.0%
3 =126 - 250	38.0%
4 =251 - 500	38.0%
5 =501 - 1000	28.0%
6 =1000+	34.0%


COVID-19 Convalescent Plasma Reduction in Death at 28 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Linear Graphing)
y = -0.0549x + 0.6053
R² = 0.8161

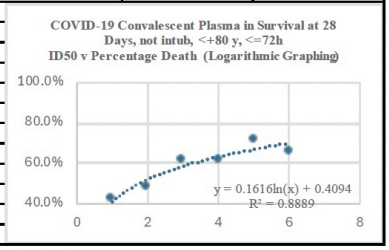
ID50	Survival
1 = 0 - 62	42.0%
2 = 63 - 125	48.0%
3 =126 - 250	62.0%
4 =251 - 500	62.0%
5 =501 - 1000	72.0%
6 =1000+	66.0%


COVID-19 Convalescent Plasma in Survival at 28 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Linear Graphing)
y = 0.0549x + 0.3947
R² = 0.8161

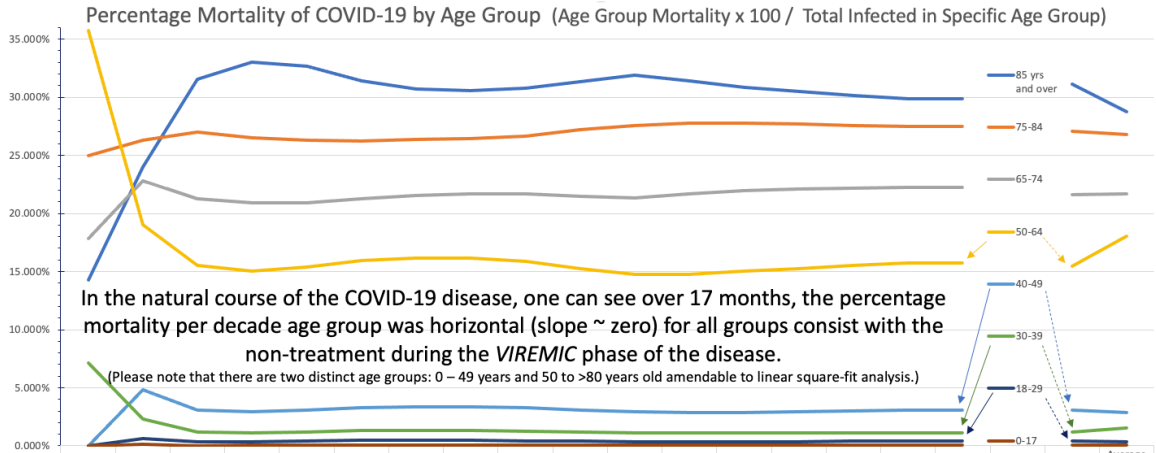
ID50	Death
1 = 0 - 62	58.0%
2 = 63 - 125	52.0%
3 =126 - 250	38.0%
4 =251 - 500	38.0%
5 =501 - 1000	28.0%
6 =1000+	34.0%


COVID-19 Convalescent Plasma Reduction in Death at 28 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Logarithmic Graphing)
y = -0.162ln(x) + 0.5906
R² = 0.8889

ID50	Survival
1 = 0 - 62	42.0%
2 = 63 - 125	48.0%
3 =126 - 250	62.0%
4 =251 - 500	62.0%
5 =501 - 1000	72.0%
6 =1000+	66.0%

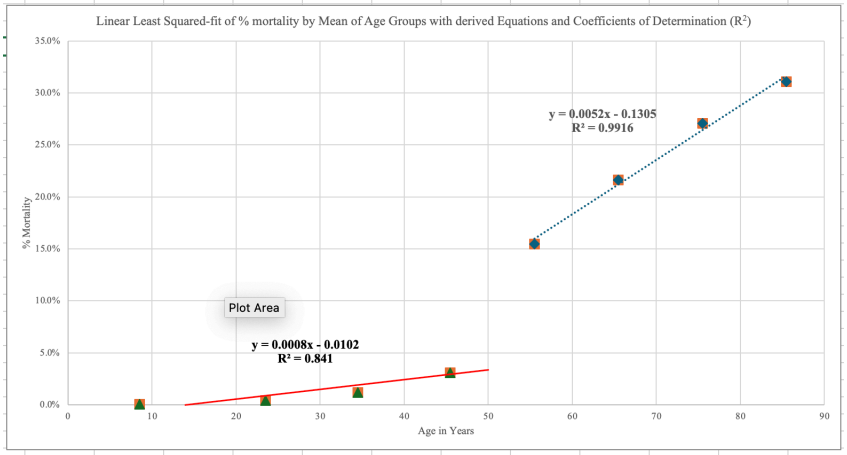

COVID-19 Convalescent Plasma in Survival at 28 Days, not intub, <+80 y, <=72h ID50 v Percentage Death (Logarithmic Graphing)
y = 0.1616ln(x) + 0.4094
R² = 0.8889

Graph IV, fig 1 and fig 2: Plots of Monthly Percentage Mortality from February 2020 to June 2021 reports of the CDC database of sex and mortality of COVID-19.[187]


Percentage Mortality of COVID-19 by Age Group (Age Group Mortality x 100 / Total Infected in Specific Age Group)
35.000%
30.000%
25.000%
20.000%
15.000%
10.000%
5.000%
0.000%
85 yrs and over
75-84
65-74
50-64
40-49
30-39
18-29
0-17
In the natural course of the COVID-19 disease, one can see over 17 months, the percentage mortality per decade age group was horizontal (slope ~ zero) for all groups consist with the non-treatment during the VIREMIC phase of the disease.
(Please note that there are two distinct age groups: 0 – 49 years and 50 to >80 years old amendable to linear square-fit analysis.)

	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-20201	May-21	Jun-21		Average from 4/2020 to present	Average from 1/2020 to the present
85 yrs and over	14.286%	23.964%	31.510%	33.007%	32.674%	31.398%	30.713%	30.536%	30.739%	31.324%	31.866%	31.378%	30.863%	30.484%	30.144%	29.874%	29.845%		31.090%	28.728%
75-84	25.000%	26.308%	26.972%	26.487%	26.277%	26.201%	26.335%	26.442%	26.671%	27.188%	27.571%	27.774%	27.779%	27.695%	27.569%	27.470%	27.463%		27.059%	26.789%
65-74	17.857%	22.763%	21.258%	20.921%	20.933%	21.276%	21.563%	21.675%	21.647%	21.472%	21.351%	21.663%	21.933%	22.098%	22.189%	22.264%	22.268%		21.634%	21.674%
50-64	35.714%	19.023%	15.528%	15.064%	15.367%	15.947%	16.148%	16.127%	15.857%	15.236%	14.728%	14.784%	15.019%	15.247%	15.517%	15.725%	15.750%		15.470%	18.016%
40-49	0.000%	4.843%	3.099%	2.964%	3.083%	3.318%	3.387%	3.376%	3.294%	3.098%	2.937%	2.885%	2.895%	2.944%	3.013%	3.065%	3.070%		3.095%	2.848%
30-39	7.143%	2.331%	1.218%	1.146%	1.216%	1.334%	1.327%	1.318%	1.282%	1.203%	1.111%	1.089%	1.085%	1.099%	1.125%	1.149%	1.149%		1.190%	1.518%
18-29	0.000%	0.656%	0.382%	0.369%	0.402%	0.469%	0.469%	0.467%	0.453%	0.421%	0.385%	0.376%	0.377%	0.382%	0.390%	0.399%	0.400%		0.409%	0.378%
0-17	0.000%	0.112%	0.034%	0.041%	0.048%	0.057%	0.058%	0.059%	0.059%	0.057%	0.051%	0.050%	0.050%	0.051%	0.053%	0.054%	0.055%		0.052%	0.049%

Fig 1: Y axis = monthly decade age group mortality due to COVID-19 total population of decade age group, Y axis = mortality rate in %. Data derived from the CDC database of sex and age mortality.
https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge [187]


Linear Least Squared-fit of % mortality by Mean of Age Groups with derived Equations and Coefficients of Determination (R²)
% Mortality
Age in Years
y = 0.0052x - 0.1305
R² = 0.9916
y = 0.0008x - 0.0102
R² = 0.841
Plot Area

0 – 49 years of age: Mortality rate (y) = 0.0008 (x) – 0.0102 $r^2 = 0.84$

50 – 90+ years of age: Mortality rate (y) = 0.0052 (x) – 0.1305 $r^2 = 0.99$

Fig 2 is derived from a calculated least-square fit of the data from Fig. 1. The slopes of the plots x 100 equals the fractional increase in mortality rate per year for the 0 – 49 age group of roughly 0.08% increase per age-year of the annual mortality and for the ≥50 age mortality of 0.52% increase per age-year of the annual mortality of ages are: 50 years of age, the calculated risk of mortality rate is: [(0.0052 x 50)-0.1305= 14%; 60 years of age, the calculated risk of mortality rate is: [(0.0052 x 60)-0.1305] = 18.2%; and 70 years of age, the calculated risk of mortality rate is [(0.0052 x 70)-0.1305]= 23.4%.

The cornerstone of U.S. Medicine's denial of COVID-19 Treatment for all regardless of age or concomitant chronic illnesses (vs. Prophylaxis) in the addressing of COVID-19 was the need to discredit the usefulness of early (with 72-96 hour) administration of exogenous immunoglobulins (***Passive Immunization***) and antivirals during the viremic phase[186] to ALL who became infected with coronavirus, SARS-CoV-2. This is a foundational immunologic postulate regarding the effectiveness of **Passive Immunization** and antiviral therapies:

Table 4: Updated Evidence to Support the Emergency Use of COVID-19 Convalescent Plasma – as of 9/23/2020.[167]

Updated Evidence to Support the Emergency Use of COVID-19 Convalescent Plasma – as of 9/23/2020														
BEST ITERATIONS	**7-day**							**28-day**						
	Lived 7-day	**Survival**		**Death 7-day**	**Mortality**		**p value**	**Lived 28-day**	**Survival**		**Death 28-day**	**Mortality**		**p value**
Low titer Not Intubated	1002	***86.08%***		162	13.92%	1164		312	***50.24%***		309	49.76%	621	
High titer Not Intubated	1178	***88.97%***		146	11.03%	1324		360	***58.35%***		257	41.65%	617	
	2180			308		**2488**		672			566		**1238**	
FDA reported							0.03							0.004
Iterated							0.0326							0.0044
	Lived 7-day	**Survival**		**Death 7-day**	**Mortality**		**p value**	**Lived 28-day**	**Survival**		**Death 28-day**	**Mortality**		**p value**
Low titer Not Intubated, ≤80 y, ≤72 h	408	***88.70%***		52	11.30%	461		130	***53.50%***		113	46.50%	243	
High titer Not Intubated, ≤80 y, ≤72 h	442	***93.64%***		30	6.36%	471		161	***66.53%***		81	33.47%	242	
	850			82		**932**		291			194		**485**	
FDA reported							0.008							0.004
Iterated							0.0079							0.004
https://www.fda.gov/media/142386/download														

Discussion:

U.S. Medicine's response in the treatment (not prophylaxis) in the United States epidemic of COVID-19 was disorganized, leaderless, downright slopy, and highlighted our failure to remaining true to our Hippocratic Oath: *Primum non Nocere* – First, do no harm.[197] The NIH (especially the NIAID), the FDA, the CDC, the PHS, the VA, U.S. Academic Medicine, medical publications like JAMA and NEJM, etc. should be ashamed for not developing, appropriately publicizing, and universally implementing an organized approach to the early treatment (≤ 72 hours of diagnosis/symptomatology) by utilizing (1.) ***Passive Immunization*** [16,22,33-38, 46,47,127, 190, 198-201] **synergistically**[129,196,202-204] with (2.) **antivirals** [16,37,128-130,145,148-157,186,196,202-211] in the drive to mollify the severity outcomes of coronavirus, SARS-CoV-2, COVID-19 infections in all newly-infected individuals. For all non-infected individuals, ***Active Immunization*** [10-14,16,35,127] (vaccination) should be universally administered; and, if ***Passive Immunization*** was given previously to those acutely infected with COVID-19 or having sustained close-contact exposure, then subsequent *Active Immunization* (vaccination) should be administered ~8 weeks later.

While alluded to throughout the last five years, **no organized, statistically-significant protocol** for the early treatment (≤72 hours from diagnosis/symptomatology) was championed or implemented by U.S. Medicine. For over a century though, early treatment (within 72 hours of diagnosis) of the viral-naïve, acutely-infected individual with the use of exogenous immunoglobulins (***Passive Immunization***) and **antivirals** have been and should be the Standard of Care. Throughout the last century, the fundamentals of the acute Treatment (not Prophylaxis) of Infectious Diseases are based foundationally on three concepts:

1. Antibiotics and Antivirals administered with multiple doses over 5 to 10 days ASAP

2. Exogenous Immunoglobulins, e.g.: convalescent plasma and sera, gamma-globulin, IVIG, polyclonal antibodies, monoclonal antibodies, etc. [single dose (if adequate high-titer) – the *Magic Bullet* theory[38,212] versus multiple doses of low-titer to summate to high-titer dosing ($C_1 \times V_1 = C_2 \times V_2$)].

   The simple titration equation: $\mathbf{C_1 \times V_1 = C_2 \times V_2}$ or, in terms of exogenous immunoglobulins:

   $$\mathbf{Antibody\ titer_1 \times Volume_1 = Antibody\ titer_2 \times Volume_2},$$

   can be used to calculate a cumulative total high-dose administration using multiple doses of low-titer CCP where C is the concentration of a solution (e.g.: moles of substance, titers of antibodies, etc.) and V is volume of the solution (e.g.: ml, L, oz, etc). The equation above is the mathematical construct for the basis of all titrations--including Clinical Immunology:

Conversion Low Dose COVID-19 Convalescent Plasma to High Dose COVID-19 Convalescent Plasma (CC-FFP) by increasing administration volume[Ref 93, page 29]:

Titer of a Dose (200 ml) of CC-FFP	**C1:** Relative Polyclonal Antibody Units (RPAU)	**V1: Std Volume** of CC-FFP (200 ml = 1/2 unit of CC-FFP)	**C1 x V1= RPAU x 200 ml STD RPAU in STD VOL**	**C1 x V2= RPAU x 400 ml**	**C1 x V2= RPAU x 800 ml**	**C1 x V2= RPAU x 1600 ml**
		std dose vol	***RPAU x 200 ml= 1/2 unit of CC-FFP***	***RPAU x 400 ml = 1 unit of CC-FFP***	***RPAU x 800 ml = 2 units of CC-FFP***	***RPAU x 1600 ml = 4 units of CC-FFP***
Very low titer -- <1:80 dilution	<80					
Low titer -- 1:80 dilution	80	200	16,000	32,000	64,000	128,000
Low titer -- 1:160 dilution	160	200	32,000	64,000	128,000	256,000
Low titer - 1:320 dilution	320	200	64,000	128,000	256,000	512,000
High titer -- 1:640 dilution	640	200	128,000	256,000	512,000	1,024,000
High titer -- 1:1280 dilution	1280	200	256,000	512,000	1,024,000	2,048,000
High titer -- ≥ 1:2560 dilution	2560	200	512,000	1,024,000	2,048,000	4,096,000

Based on the FDA presentations of August 23, 2020 and September 23, 2020.[166-167]

3. Optimization of Synergy of antibiotics or antivirals with exogenous immunoglobulins (versus the humanly-inherent naïve wish of *The Magic Bullet* of one agent and one time only.

A. **Active Immunization:** Administration of exogenous specific **antigens (Ag)** by vaccination to produce endogenous **antibodies (Abs)** in the non-infected individual against those specific antigens (Ag). Normally, what is thought of as a vaccination, is a stimulation within the individual of B-cell development to produce endogenous antibodies (e.g: IgM, IgG, IgA) to specific Ags presented to the individual being vaccinated. In the individual, development of IgG against some Ag of the COVID-19 requires roughly two weeks for full effective immunologic response. With the time delay of the development of adequate amounts of endogenous IgG in the COVID-19 individual over two weeks, vaccination (Active Immunization) is *prophylaxis* limited to non-infected individuals (not *treatment* of actively, acutely infected individuals). As the most effective time of IgG viral replication-suppression is during the viremic phase of COVID-19 (<72 - 96 hours from diagnosis) and not later during the time of cytokine cascade and bradykinin storm, there is limited efficiency of *Active Immunization* when administered to acutely, symptomatic, infected individuals. Active immunization of systemic vaccines long-term act through a complex cellular/humoral mechanism to address systemically the viremia early in the course of the disease (72-96 hours) with endogenous immunoglobulins in the vaccinated individual. In the case of respiratory viruses like COVID-19, nasal resistance to the SARS-CoV-2 virus is due to the development of mucosal IgA and not due to systemic immunoglobins, IgM and IgG, previously resultant from vaccination or previous systemic infection. While mucosal IgA, requires only ~5 days after COVID-19 nasal exposure to reach adequate levels, IgA protection is limited both due to the proximity to the nares mucosa initial exposure and has a short half-life long-term thus being ineffective for subsequent exposures without nasal reinoculation.

B. **Passive Immunization:** Administration of exogenous antibodies (not exogenous antigens) to provide immediate systemic immunologic response (IgG) from a donor (convalescent plasma or serum or polyclonal antibodies, or monoclonal antibodies). Application of *Passive*

> *Immunization* is *treatment* not *prophylaxis* when administered (within 72-96 hours of diagnosis) to an newly infected individual. The *in vivo* persistence of *Passive Immunization* is dependent on the ½ decay over ~21 days and, thus, utilization of *Passive Immunization* as a prophylactic agent is limited to the ½ life decay of the exogenously administered antibodies. (See Attachment I regarding Respiratory Syncytial Virus (RSV) therapeutics) A naturally occurring form of *Passive Immunization* is the passage of maternal antibodies across the placenta to the fetus. Passive immunization when given early has been the mainstay for the treatment of infections for over a century especially when pharmacologic antibiotics or antivirals have not been available. When antiviral pharmacologic agents are available, passive immunization can also be used successfully synergistically in the viral-naïve infected individual. Convalescent plasma and sera, polyclonal antibodies, and monoclonal antibodies; γ-globulin, IVIG, etc.; and other specific plasmas and sera (Pasteur's rabies vaccine, hypertet, RhoGam, antivenoms, etc.) are all effective variations of *Passive Immunization)*

As has been extensively outlined in the **Results** section and confirmed by back-calculating iterations of the FDA's published results of August 23, 2020, and September 23, 2020, COVID-19 Convalescent Plasma when analyzed and reported by the FDA in the administrations of >94,000 units through the Mayo Clinic/FDA Protocol was statistically significant in decreasing mortality (thus increasing survival) when given in high titer administrations in less or equal to 72 hours from the time of diagnosis/symptomatology.[166-167] There are at least thirteen articles (listed below in chronological order) [168-180] that have been published from the Mayo Clinic / FDA Protocol of whom, the Principal Investigator (PI) was Michael Joyner, M.D., Ph.D. The Mayo Clinic / FDA Protocol was abruptly, inadvertently discontinued on August 23, 2020, due to the issuing of an EUA[213] regarding CCP that was headlined in *The White House* press conference directed by President Trump.[214] The universal general conclusion of reports resultant from the Mayo Clinic /FDA Protocol can be summarized in the following statement from the article[176]: Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, Grossman BJ, Henderson JP, Musser J, Salazar E, Hartman WR, Bouvier NM, Liu STH, Pirofski LA, Baker SE, van Helmond N, Wright TS, Fairweather D, Bruno KA, Wang Z, Paneth NS, Casadevall A, Joyner M: The effect of convalescent plasma therapy on COVID-19 patient mortality: Systematic review and meta-analysis. Mayo Clin Proc, 2021 May; 96 (5): 1262-1275. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7888247/pdf/main.pdf :

> CONCLUSION This real-time systematic review and metaanalysis of contemporaneous studies highlights that the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19 and suggests that **early transfusion of high-titer plasma represents the optimal use scenario to reduce the risk of mortality among patients with COVID-19.** These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent.

In the heat of the moment, though, during the terminal controversy in early 2021 over the effectiveness of early-administered COVID-19 Convalescent Plasma, Carlos H. Villa, M.D., PhD, Medical Officer, OBRR/DBCD/CRS wrote[181] to Nicole Verdun MD, Director, OBRR of the U.S. Food & Drug Administration (FDA) [the OBRR is the Office of Blood Research and Review, which is part of the Center for Biologics Evaluation and Research (CBER) within the Food and Drug Administration] acknowledging both the positives and negatives of CCP administration but **concluded that it is all about three independent variables:**

(1) the concentration of exogenous CCP
(2) the timing of administration of exogenous CCP during the viremic phase of COVID-19, and
(3) the individual human's endogenous immunological response to the infection (Table 3)

This present ***undated*** FDA memorandum[181] that can be found on the Internet is: https://www.fda.gov/media/141480/download was **an overwriting of the original document of August 2020**[182], which had been instrumental in the change of the published FDA Guidance on COVID-19 Convalescent Plasma of September 2, 2020.[215] This overwriting of the document issued in August 2020 [216] which was the basis for *The White House* press conference on August 23, 2020, directed by President Trump[164] , is confirmed as the quoted which anachronistically uses as documentation an article in the 2021 future: Lister et al[217] which ironically was published by the *New England Journal of Medicine* on the date of the June 6th, 2021 Insurrection[218]:

> Libster R, Pérez Marc, Wappner D, Coviello S, Bianchi A, Braem V, Esteban I, Caballero MT, Wood C, Berruetta M, Rondan A, Lescano G, Cruz P, Ritou Y, Fernández Viña V, Alvarez Paggi D, Esperante S, Ferreti A, Ofman G, Ciganda A, Rodriguez R, Lantos J, Valentini R, Itcovici N, Hintze A, Oyarvide ML, Etcegarary C, Neira A, Name I, Alfonso J, López Castelo R, Caruso G, Rapelius S, Alvez F, Etchenique F, Dimase F, Alvarez D, Aranda SS, Sánchez Yanotti C, De Luca S, Baglivo J, Laudanno S, Nowogrodzki F, Larrea R, Silveyra M, Leberzstein G, Debonis A, Molinos J, González M, Perez E, Kreplak N, Pastor Argüello S, Gibbons L, Althabe F, Bergel E, Polack FP, for the Fundación INFANT-COVID-19 Group*: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true Republished N Engl J Med, February 18, 2021; 384(7): 610 – 618.

This *ex post facto* reference of Villa[182] with the overwriting of the original August 2020[181] document is allegedly an illegal OVERWRITING of a Federal Policy lost to history by its inherent undated anonymity. This anachronistic OVERWRITING is a violation of the Sarbanes-Oxley Act of 2002, PL 107-204, 18 U.S.C. §1512(c)(1)[103] -- that may have innocently and publicly mollified the FDA's original position at the time in February 2021 but has covered-up for all of history and misdirected all future teachings and applications by U.S. Medicine of the clinical science of *Passive Immunization* by its undated *de facto* anonymity. The opening sentence in the June 28, 2024 opinion of the Supreme Court of the United States in Fischer v. United States[104] reiterates that it is illegal to alter, destroy, mutilate, or conceal a Federal record, document, or other object:

> The Sarbanes-Oxley Act of 2002 imposes criminal liability on anyone who corruptly "alters, destroys, mutilates, or conceals a record, document, or other object, or attempts to do so, with the intent to impair the object's integrity or availability for use in an official proceeding." 18 U.S.C. §15129(c)(1)

As was successfully promoted by the WHO in the 1970s for the complete eradication of smallpox in the 1970s, **an epidemiology of synergy** of a combination of (1) coordinated treatment of **ALL** acutely infected individuals with exogenous immunoglobins (*Passive Immunization*) and antivirals and (2) prophylaxis with vaccines (*Active Immunization*) of all non-infected individuals immediately or after a period of time (~8 weeks) if they received exogenous

immunoglobulins due to their high-risk of exposure should have been implemented in our addressing of COVID-19. [219-235] Such an epidemiology of synergistic treatment and prophylaxis should today be emulated in the now ongoing threat of M-pox (monkey pox)[236-239], in our addressing of respiratory syncytial virus (RSV) (**Attachment I**), and in treating all future viral threats. In varying degrees, the antithesis to **synergy**[129,196,202-204] in the treatment of infectious diseases is our century-old, naïve belief in the *"Magic Bullet"* [38,212] only: i.e., our expectations in the treatment of diseases are that we will find one agent that will eradicate the disease 100% of the time in the infected individual. A century ago, the Noble Prize in Medicine or Physiology was awarded to Paul Erlich in 1908 for his concept of chemotherapy (i.e.: specific chemical/drug therapy in the treatment of disease).[212] The most outstanding, successful example of the *Magic Bullet* was Sir Alexander Fleming's discovery of penicillin for which he was awarded the Noble Prize in Medicine or Physiology in 1945.[27] Our quest for magic bullets has truly advanced medicine over the last 100+ years but that very mindset of discovering the next magic bullet has also delayed the utilization of the synergistic treatment of diseases with combinations of somewhat-less-than-effective single magic bullets at the same time—even, though, such synergy may be much more clinically successful than any single magic bullet.[240-242] Some examples of synergistic treatment of infectious diseases in the present day include, e.g.: the treatment of gram negative organisms, tuberculosis, drug resistant microbes, HIV, hepatitis C, etc. The synergistic use of antivirals, immunotherapy, and immunomodulation has been suggested to be most successful in COVID-19 especially when given during the viremic phase of the disease (roughly less than 72 hours from diagnosis/symptomatology).

There is a trail of clinical-treatment-policy missteps which would be sadly comical if there was not cumulative layers of disregard and blatant contradiction to medical fundamentals, chronic denial (Attachment V), political self-centeredness, narcissism, ignorance bordering on stupidity, and just-plan meanness that were put-in-play in March/April 2020, that has continued over the last five years, and are still perpetuated into the future. A summary of COVID-19 pathophysiology and an abbreviated timeline of immunoglobulin and antiviral therapy can be found in:

> Andrus CH: Book 4: President Biden's July 7, 2023 Response Letter to Dr. Andrus' submission of 2023-04-27 update 11-7-13.pdf. 0.2 2022-09-11 Dear Mr President Case Report and COVID-19 pathophysiology. 1 – 74 pages. https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp 2024-03-05, e56 – e130. [93]
>
> > On July 7, 2023, President Joseph Biden replied to the included summary submission of Book 1: Dear Mr. President: COVID-19 and Where We Went Wrong. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02/ [85]
> >
> > Book 1 is 1266 pages documenting correspondence with the NIAID, the FDA, the VA, and The White House over 3 years concerning the clinical care of patients newly infected with COVID-19. All the documentation that has been submitted to the NIH NIAID Case #12276 (Book 1 is an abridged documentation) is available through the Freedom of Information Act Officer of the NIAID. The submissions to the NIAID and FDA in detail outlined the pathophysiology of coronavirus SARS-CoV-2; the difference between Active Immunization (vaccination for PROPHYLAXIS to stimulate endogenous immunoglobulins) vs Passive Immunization in the TREATMENT of acute COVID-19 within 72 - 120 hours of diagnosis] through the administration of exogenous immunoglobulins, e.g.: Convalescent Plasma, Monoclonal Antibodies, and Monoclonal Antibody cocktails, etc.); describe extreme misinformation and obfuscation by the NIH, NIAID, FDA, etc.; describe in-depth the inappropriate late timing of administration of immunoglobulins and antivirals (>120 hours from diagnosis of acute infection); and the cover-up by governmental, academic, etc. entities by electronic overwriting, URL site relabeling/renaming, and website removal; officials,medical researchers, academics, and clinicians, and agencies advancing incorrect or misleading medical statistics and theories that were associated with and were possibly contributory to >1,000,000 reported deaths from COVID-19 in the U.S.A. from March 2020 to the present. -- Charles H. Andrus, M.D., F.A.C.S.

Throughout March 2020, six misadventures in the (1) treatment implementation, (2) subliminal withholding or rationing of treatment implementation, (3) an establishment of general therapeutic abandonment policy and treatment, and (4) unintentional denial of patient rights set the stage for all that would follow:

1. **March 2, 2020, The Outline of Addressing the U.S. response to the COVID-19 Pandemic**: At the meeting in *The White House* between the President and Vice-President of the United States and Federal Physicians who would become members of *The White House* Commission on the COVID-19 and representatives of Pharmaceutical / Biologics Corporations (Table I), the concept of early treatment (<72 hours) with *Passive Immunization* and *Antivirals* was minimized in favor of primarily rapid vaccine (*Active Immunization*) development and deployment throughout the nation. With the absence of representation of the American Red Cross and the American blood banks, and the following euphemistic misstatement regarding *Passive Immunization*,

   2020-03-02 The White House: Remarks by President Trump and members of the coronavirus task force in meeting with pharmaceutical companies.
   1.) Transcript: https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/
   2.) Entire meeting video: https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus:
   3.) Video of Dr. Schleifer's euphemistic explanation of *Passive Immunization*: https://www.youtube.com/watch?v=31i6p_stzW8:

   > DR. SCHLEIFER: Thanks, Mr. President, for having us. I'm Lenny Schleifer, the founder and CEO of Regeneron, a company that I built with George Yancopoulos over the last 30 years. And we are a monoclonal antibody primarily centered company. We are no strangers to collaborating with the administration. We work with Secretary Azar's group, BARDA. And we came up with a cure for Ebola, and we're very proud of that. Dr. Fauci's group was really instrumental in testing that under unbelievable conditions in the Congo. And it didn't create quite as much excitement, because, thank goodness, it didn't hit our shores.
   >
   > But we can use the exact same technology, and we already have. We have 1,000 antibodies that are already sitting in dishes. We're screening them. We're selecting them. We anticipate, if all goes well, 200,000 doses per month can come out of our factory in New York, starting in August.
   >
   > The unique thing about our technology —
   >
   > THE PRESIDENT: That means you'd be able to use the vaccine that early?
   >
   > DR. SCHLEIFER: It depends on what we see; how we work closely with the FDA, which we will do. The FDA already reached out to us, but we've got to work closely.
   >
   > THE PRESIDENT: So that process would be faster than John's?
   >
   > DR. SCHLEIFER: It would be. The —
   >
   > SECRETARY AZAR: Can you explain why that would be?
   >
   > DR. SCHLEIFER: Well, so, we make **passive vac- — vaccine** and therapeutic — therapeutic. Our drug will be able to protect you. Whether or not you're infected, it'll protect you from getting infected. Or if you are infected, it would treat you. And the — we have just taken processes that normally take years — literally, years — and we put them end-to-end and now do them in weeks to months, which nobody else in the industry can do.
   >
   > So we're very excited to collaborate once again.
   >
   > THE PRESIDENT: So this would be a combination of a vaccine and also it will — to put it in a different way — make you better, quicker.
   >
   > DR. SCHLEIFER: Yeah. Well, think of it this way: If you — if you get immunized with one of these vaccines, you're going to make some antibodies to protect you. We're going to already make those antibodies and give them to you so you don't have to go through that whole process. So it'll protect you.
   >
   > And, as we showed with Ebola, if you give enough of them — we — it was lifesaving, life- — truly lifesaving.
   >
   > THE PRESIDENT: That's true.
   >
   > DR. SCHLEIFER: And it beat out the antivirals. It really — it was the way to go. It's very predictable.

> I just want to say, I hope everybody succeeds here. I mean, this is — bringing everybody together here is really critical and there's going to be success. This industry is really talented, as an industry. Sometimes we run astray, but we're going to get this done.
>
> THE PRESIDENT: Thank you very much. Thanks, Len. Appreciate it. Please.

the future American public and medical mindset became tainted with the minimization of the ethical importance of early-in-the-course-of-the-disease treatment (<72 hours from diagnosis) **SYNERGITICALLY** with immunoglobulins (*Passive Immunization*) and antivirals for ***ALL*** acutely infected with coronavirus, SARS-CoV-2, versus therapeutic abandonment favoring instead prophylaxis of the "herd" with anticipated vaccines (*Active Immunization*) and mass inoculations in the future.

2. **March 13, 2020: Proclamation of the Public Health Emergency (PHE):** xxx
3. March 17, 2020: Suspension of parts of EMTALA
4. March 18, 2020: Surgeon General advocates staying away from hospitals
5. March 24, 2020: EUA regarding Convalescent Plasma with rationing criteria is announced by the FDA
6. March 26, 2020: The British Medical Journal (BMJ) documents rationing criteria. Due to the removal/overwriting of the URLs, all three references point to *ex post facto* sources
7. April 4, 2020: Michael Joyner, M.D., PhD, becomes the Principal Investigator of the Mayo Clinic /FDA COVID-19 Convalescent Plasma program
8. May 1, 2020: EUA for Remdesivir

7.0 2021-09-19 Timeline of U.S. Government Regarding Passive Immunization and the Discrediting of COVID-19 Convalescent Plasma is a more complete outline sent to President Biden in September 2021.[37 pages 290-292]:

Dear Mr. President:

Please excuse my forwardness in submitting this cover letter to you but it is of major importance and my duty as a federal physician to appraise you of this. As Dr. Birx said in her interview with Margaret Brennan on face the nation on January 24, 2021, this may never come out in her lifetime. The bottom line is that US medicine and the executive branch of the federal government in March 2020, abandoned the America people by NOT offering **Passive Immunization** as the immediately available treatment of COVID-19, future synergistic treatment with **Active Immunization** in all that contract COVID-19 after vaccination, and a prophylaxis for high-exposure individuals like healthcare workers, first responders, grocery clerks, immune suppressed individuals and everyone else. The timeline of the failure of U.S. Medicine, U.S. Research, and the U.S. Government regarding **Passive Immunization** is as follows:

1. On March 3/2/2020, leaders of Pharma, the FDA, the NIH, etc. met with President Trump and failed to make the distinction of **Active Immunization versus Passive Immunization.** https://www.youtube.com/watch?v=31i6p_stzW8

2. President Trump declared an emergency on March 13, 2020. https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/
3. Secretary Azar on March 13, 2020 suspended parts of EMTALA retroactive to March 1, 2020. https://www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx
4. China sends medical team to Italy to set up 50 blood collection centers to help in treatment of COVID-19. https://www.chinadaily.com.cn/a/202003/14/WS5e6bd352a31012821727f096.html
5. On March 19, 2020, Johns Hopkins Bloomber School of Public Health carries story of China offering to Italy 90 tons of COVID-19 Convalescent Plasma (~500,000 doses). https://www.globalhealthnow.org/2020-03/covid-19s-stop-gap-solution-until-vaccines-and-antivirals-are-ready
6. On March 24, 2020, **FDA Failure because** instead of the FDA declaring **Passive Immunization** synergistic with future vaccination (active immunization--vaccination) and declaring convalescent plasma (a Nobel Prizing winning passive immunization, 1901) a biosimilar biologic to e.g.: rabies vaccine, RhoGAM gamma globulin, IVIG, tetanus hyper immune globulin, etc., the FDA **declared COVID-19 convalescent plasma investigational**. (i.e.: **EXPERIMENTAL**) https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf
7. In order to make convalescent plasma immediately available the FDA authorized **expanded access** (**COMPASSIONATE USE**) through six programs in the United States WITH most visible that through the Mayo Clinic in which over >2700 hospitals would participate. https://web.archive.org/web/20200404010134/https:/www.uscovidplasma.org/ By the definitions of the NIH and FDA "Expanded Access" is "Compassion Use" (DATA NOT AVAILABLE TO BE USED FOR CLINICAL TRIALS) which means that any data from the administration of over 94,000 doses by the Mayo Clinic from March 24, 2020 to EUA of August 23, 2020 should not have been used as data for research studies. (The vast majority of **CCP administrations were given late in the disease at the WRONG TIME.)**
8. On March 24, 2020 the FDA announced inclusion criteria for administration of COVID-19 convalescent plasma which was wrong giving it only when the patients were on death's door with the FDA referencing their misinterpretation of an Chinese epidemiology paper published in February 2020. (**The FDA removed the reference in all subsequent documentations and failed to tell the American public they were administering CCP at the WRONG time.** The FDA quietly removed the WRONG inclusive criteria from all subsequent documentation on September 2, 2020.) Passive immunization has only been shown to be most successful in previous epidemics when given within the first 72 hours of diagnosis—NOT at death's door! https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf
9. **For the last 18 months the FDA has made all the agents of passive Immunization experimental (Investigational) by issuing EUAs.** In so doing they violated the intent (and really the letter of the law) of PL-115-176, the Right to Try Law

https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf in limiting the ability of patients to request **Passive Immunization** agents –thus, abandoning / withholding treatment of the American people within 72 hours of contracting COVID-19.

10. CCP was issued its first EUA on August 23, 2020 while still under the restrictive late-in-the-disease inclusion criteria of March 24, 2020. The FDA quietly rescinded this wrong inclusion criteria on September 2, 2020 and then did not notify the American public. (The FDA also quietly rescinded the same inappropriate inclusion criteria regarding Remdesivir on August 28, 2020.). President Trump in the first 2 minutes of the White House Press Conference insulted China by referring to the coronavirus SARS-CoV-2 virus as the **CHINA virus**. (China stopped their epidemic by quarantine and liberal use of CCP. How does one know this?--In March 2020, China sent 15 medical personnel to Italy to assist in the development of CCP infusion centers and **China offered 90 tons of surplus CCP to the Italians.**)
11. October 2, 2020 President Trump was diagnosed with COVID-19, and within four hours President Trump was given Regeneron monoclonal antibody cocktail and within 18 hours began Remdesivir infusions. Subsequently, it is documented that former Governor Christie, former Mayor Giuliani, and former HUD Secretary Dr. Ben Carson received at least monoclonal antibodies. **While every person in the United States who turned positive for COVID-19 should have been eligible for early administration of this combination of monoclonal antibodies and Remdesivir, it was concealed in plain sight** from the American people by agencies of the Executive Branch of the Federal Government by not announcing its significance formally to the American people.
12. In November 2020 the VA issued the incorrect timely--administration inclusion criteria for Remdesiver (Velkury), which had been approved as a prescription drug on October 22, 2020 by the FDA. The VHA still lists this incorrect administration criteria continuing to this day on the Internet to this day. At the time, I was in e-mail communications with VHA Chief Medical Executive, Richard Stone, M.D., (really VHA Under Secretary of Health although I am not sure he was approved by Congress) and *The New England Journal of Medicine*.
13. On January 6, 2021, *The New England Journal of Medicine* published the **only prospective, randomized, placebo-controlled, appropriately timed (<72 hours from diagnosis administration), age-stratified CCP administrated article** for the last 18 months. This "landmark" article definitively demonstrated that when CCP was administered early (<72 hours from time of diagnosis) and compared with placebo in 70 year old patients, the decrease in hospitalization was significant ($p< 0.03$) and the morality was halved (CCP=2 vs. placebo=4) but did not reach significance as the study was too small.
14. On January 24, 2021, Dr. Birk's was interviewed by Margaret Brennan on *Face the Nation.* https://www.youtube.com/watch?v=odklJGnhvhU
15. On February 1, 2021, I e-mailed the FDA, NIH, *The New England Journal of Medicine*, and many pertinent persons (*reducio-ad-absurdum*) pointing out Dr. Birk's plea.
16. On February 4, 2021, the chief scientist of the FDA, RADM Denise Hinton issued a new EUA for Convalescent Plasma (*vis-a-vis* coinciding within 48 hours of my letter to Dr. Birx).

17. Within 24 hours, Peter Marks, M.D., Chief of the Biologic Division of the FDA is quoted in the WSJ with conflicting remarks about convalescent plasma. He then issues an official statement from the FDA and in an interview three weeks later praising CCP.
18. In the NEJM on February 18, 2021, Dr. Katz Acting Director of the Mississippi Valley Blood Authority (now renamed ImpactLife) prints a three page light-hearted, obfuscating editorial entitled: (A Little) clarity on convalescent plasma for COVID-19.
19. In February 2021, BARDA announces it will defund CCP throughout the nation.
20. March 8, 2021, ImpactLife to phase out CCP donations (~120 hospitals in the Midwest)[484]
21. The NIH quotes an underpowered study (results not published) regarding a non-age-stratified placebo-controlled ER study on CCP administration that was closed early because they could not recruit even patient's for the placebo study.
22. March 10, 2021: Convalescent Plasma Strikes Out as COVID-19 Treatment. https://www.npr.org/sections/health-shots/2021/03/10/975365309/convalescent-plasma-strikes-out-as-covid-19-treatment
23. April 21, 2021: NIH COVID-19 Treatment Guidelines panel recommends against COVID-19 Convalescent Plasma. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/convalescent-plasma/
24. Regeneron teams up with ROCHE International to market REG-CoV-2 (monoclonal cocktail to the world). (ROCHE is selling REG-CoV-2 to Indian hospitals for 50,000 Repees (~$800) for those that can afford it to be given early in the course of the disease. On-the-street it is referred to as the "Trump cocktail")

---this outline is incomplete but is included as it is an extensive timeline on how COVID-19 Convalescent Plasma was discredited from March 2, 2020 to April 2021.

The timeline of the failure of U.S. Medicine, U.S. Research, and the U.S. Government regarding **Passive Immunization** can be found in Table 1 regarding CCP and that for the antiviral Remdesivir: Andrus CH: *Dear Mr. President: COVID-19 and Where We Went Wrong*. *Internet Archive*, publication date 2023-09-12, pages e9 – e14. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02 [37]

There are already several books by individuals and groups rendering their versions of what transpired over the course of the American COVID-19 epidemic, where we went wrong, and how we should fix our failures in the future, e.g.:

1. Gottlieb S, Former FDA Commissioner: *Uncontrolled Spread—Why COVID-19 Crushed Us and How We Can Defeat the Next Pandemic*. New York: HarperCollins Publishers, 2021. https://www.harpercollins.com/products/uncontrolled-spread-scott-gottlieb?variant=41042025545762 [243]

2. Nash DB, Wohlforth C: *How COVID Crashed the System—A guide to fixing American Health Care*. Lanham, Maryland: Rowman & Littlefield, 2022.

https://rowman.com/ISBN/9781538164259/How-Covid-Crashed-the-System-A-Guide-to-Fixing-American-Health-Care [244]

3. The COVID Crisis Group: *Lessons from the COVID WAR—An investigative report*. New York: PublicAffairs, 2023 April 25. https://www.hachettebookgroup.com/titles/covid-crisis-group/lessons-from-the-covid-war/9781541703803/?lens=publicaffairs [245]

The real tragedy in the American fight throughout the COVID-19 epidemic was that it was: (1) permeated with panic; (2) riddled with misinformation; (3) inappropriately politicalized with the notion that money can buy a cure, e.g.: Operation Warp Speed; (4) generalized inappropriate rationing based on age, concomitant diseases, etc.; and (5) lacked any organizational leadership and direction. Medically addressing a novel viral disease (i.e.: COVID-19) in the treatment of **EVERY** infected individual should be the highest priority for developing and implementing the science into foundationally anchored clinical methodologies. In short, the clinical response that should be afforded every potential and every infected patient should not be clouded in the intricacies of the molecular virology, overwhelmed by epidemiological theories, distracted by political or capitalistic philosophies, or consumed in frivolous rhetoric and *ad hominum* blame:

1. **Identify the agent** (i.e.: coronavirus, SARS-CoV-2, COVID-12) and elucidate the **pathophysiology of the disease** [e.g.: passage through the nares; entry into the pneumonocytes via the ACE-2 receptor; early development of the bilateral pneumonia symptomatology; the finite delay--which is a host rate-limiting-step--of developing adequate therapeutic serum titers of endogenous IgG (~2 weeks after contraction of the virus); the later-in-the-disease intrinsic activation of the cytokine cascade; the bradykinin storm in COVID-19 due to the affected renin-angiotensin system (RAS), etc.] **as it is related to the clinical disease**, etc. Within this initial first step, there is a constellation of processes and methodologies required:

    a. Identify the mode of transmission(s) and establish practices of epidemiological protection: quarantine, isolation, PPE, masks based on the size of the virus, method of entry into the host, etc.—e.g.: (N95 masks mean that 95% of particles under 300 nm in size will be stopped; but COVID-19 is measured to be 80 – 120 nm in size.)

    b. Develop testing methodologies that are reliable, easily deployed, and ideally meet a 0.95 confidence-level for sensitivity criteria of such “screening” tests for the populous. Using the AI program Perplexity, a summary of published sensitivities of the COVID-19 screening tests are outlined regarding RT-PCR, rapid antigen tests, and viral cultures. (**Attachment Q**)

2. Initiate Treatment:
    a. Immunotherapy
        i. Exogenous immunoglobulins as Passive Immunizations in both frontline treatment (within 72 hours of diagnosis/symptomatology) in infected patients (including previously vaccinated patients with symptomatology)

and in the treatment and prophylaxis of immunosuppressed patients, asymptomatic but infected patients, e.g.:

1. COVID-19 Convalescent Plasma and Sera
2. Monoclonal Antibodies and Monoclonal Antibody combinations

ii. Exogenous antigens as Active Immunizations (vaccinations) in the prophylaxis for all immunological-naïve, non-infected individuals by stimulating the endogenous immune system of the patient

b. Antiviral therapy in ALL infected patients regardless of their previous vaccination status, e.g.:
   i. Veklury (Remdesivir)
   ii. Paxlovid
   iii. Etc.

c. Supportive therapy: ventilators, ECMO, resuscitations, all ongoing care, etc., etc., etc.

d. Chronic care.

3. Prophylaxis (Active Immunization/vaccination) for treatment of the "herd" of the American population which will prophylactically diminish future severity of illness, decrease the overall individual vector prevalence

In the end, U.S. Medicine in the treatment of those infected with COVID-19 was defeated by a non-sentient, non-living, complex chemical pathogen called coronavirus, SARS-CoV-2, COVID-19. We, as members of U.S. Medicine, failed at seemingly every turn:

> We failed to bridge the gap between basic science and clinical medicine.[246]
>
> We failed to base treatment on the pathophysiology of the disease.[247]
>
> We failed to set our promise of *Primum non Nocere* for each and every infected patient in not promoting an appropriate treatment plan in ≤ 72 hours from diagnosis with exogenous immunoglobulins and antivirals for ALL (regardless of concomitant risk-factors or age) infected with SARS-CoV-2, COVID-19.[197]
>
> We lied to ourselves when it was self-beneficial--reflective of our self-centeredness—we repeatedly committed the seven deadly sins of medicine.[248-249]
>
> We were not true to ourselves and we covered it up with *Chronic Denial*. [Attachment V,122-124]
>
> All of you, as physicians, should have had the fundamental knowledge regarding early treatment (≤72 hours from diagnosis) of a novel virus with antivirals and synergistically with exogenous immunoglobulins.

Throughout this analysis, I have tried to emphasize that's the treatment of any novel virus of which we have no vaccine is still accomplishable if done within 72-96 hours of diagnosis with some form of exogenous immunoglobulins and synergistically with antivirals. Literally, after writing the FDA, the NIAID, the CDC, *The New England Journal of Medicine*, The VA, the

White House,etc. since April 5, 2020, it should be personally comforting to know that all final official admonitions are consistent with what I have written.--Well, it is not. It is truly sad that in the education of future generations of physicians and surgeons throughout the world, but especially in the United States of America, we have failed in organized instruction to teach and integrate basic science tenets in clinical practice that have their origins in the late nineteenth century. The teaching of fundamentals are seemingly separated from clinical practice by distances and depths akin to that seen between the South and North Rims of Grand Canyon National Park. The major Internal Medicine textbook, *Harrison's Principles of Internal Medicine*[250], is probably not purchased by the vast majority of medical students today because they just don't purchase nor read hardcopy medical books anymore:

> As one student said to me during a junior surgery class lecture on fluid and electrolytes several years ago—I don't need to pay attention because I can find it on my iPhones.

Today, our Medical Students aren't tested on their individual fund of knowledge developed from reading a textbook but rather on the abbreviated individual course syllabus or outlines, etc. In fact, at best, the present two volume *Harrison's Principles of Internal Medicine*[250] is outstanding for pressing flowers! The medical student in many cases is never taught to analytically integrate fundamental knowledge into clinical practice because the fundamental knowledge provided is in a confused, disorganized, piece-meal manner.—Teaching at the Bedside has become haphazard at best, if not, completely passé.[251]

With regards to immunotherapies in the treatment of novel viral diseases, medical students to practicing clinicians and the American public in general today are receiving their disjointed pharmacology training and integration with clinical medicine by being inundated with disjointed, paltering advertisements on television. What is needed is a new Flexner Report[252]—for Medical Schools, Residencies, and Academic, Research, and Clinical Practice. No one need worry, though, such a revolution in American Medicine will probably never occur--for few medical students, residents, and practicing clinicians today even know the history of the scientific development of American Medical Schools and Residencies beginning in the 1880's and its integration with clinical practice dating back to Johns Hopkins University and Sir William Osler, M.D. and William Stewart Halsted, M.D., F.A.C.S.[251]

We live in the time of Machiavellianism: *The end justifies the means*.[253] If we do not have fundamental guidelines that can be implemented in daily practice that are taught to neophytic physicians and surgeons of medicine based on foundational guidelines, analytical integration, and focusing on the individual care of every patient that presents, we, as clinicians of the humanity's most noble practice for eternity, have failed our trainees.

The *New England Journal of Medicine* (NEJM) speaks of the need for integrity in publishing medical articles.[80] It is my worry that NEJM will not publish this present article because it addresses the gaping holes in our medical training, the deep-divide between research and clinical Medicine today, and the disinformation of lies of commission, omission, and paltering that are pervasive throughout our society. Throughout our society especially in the Medical Science, fact and fiction have become blurred and fiction is entertained as a reasonable alternative. In my opinion, the previous Trump Administration and its COVID-19 White House Task Force[254] in the index month of March of 2020 did a tremendous disservice to humanity as outlined above. The

concept of the single "Magic Bullet" in Medicine should go the way of the Dodo bird replaced by synergistic treatments.

In a collective subliminal validation of the application in clinical medicine of scientific foundational principles, the Mayo Clinic, the FDA, the NIH, and individuals like Dr. Birx, Dr. Fauci, Dr. Joyner, Dr. Casadevall, etc. all professed the answer in improved, consistent survivability in **the treatment** of COVID-19 (and, against all present and future viruses in which the individual is immunologically naive):

1. The initial treatment with exogenous immunoglobulins (***Passive Immunization*:** Convalescent Plasma / Polyclonal Antibodies, Monoclonal Antibodies, combinations of Monoclonal Antibodies, etc.) given to every infected individual within 72 hours of symptoms and diagnosis—over and over, again—thus, titrating to high titers in every infected individual commensurate to the antigens levels present in every infected individual.
2. Synergistic application with antivirals when available.

For survival of humanity long-term, the provision of vaccines as prophylaxis, ***Active Immunization*,** should be administered throughout the World to all:

1. live homologous virus vaccines, e.g. vaccinia
2. attenuated live vaccines, e.g., Sabine polio vaccine
3. killed whole vaccines, e.g. Salk vaccine
4. mRNA vaccines, e.g. COVID-19 vaccines

So what are the tangible things that can be initiated upon completion of reading this paper?:

1. Much like the Flexner Report of over a century ago[252], U.S. Medicine must take a hard look at reinvigorating an analytical, Scientific-Mindset in its application throughout clinical Medicine

2. Every physician and surgeon should reflect and recommit to the absolute truism of the all clinicians of all ages[255-256]:

   "… the secret of the care of the patient is in caring for the patient."

3. As Anthony Fauci MD has stated that he has been a named editor of *Harrison's Principles of Internal Medicine*[250] for 40 years[183] (11 times as a named editor and twice as the editor-in-chief), we should ask of him that he direct a major rewrite regarding how we teach the practice of medicine ongoing to all physicians who should be students of medicine for the rest of their lives—especially, in the treatment of viral diseases with exogenous immunoglobulins and antivirals (not just prophylaxis with vaccination). Consistent with a traditional full two-years in-depth study of the basic sciences in Medical School education in all U.S. Medical School, studies should be mandated with testing from hardcopy textbooks (not *de* facto electronic "cliff" notes and lectures) and then subsequent integration into the clinical years of medical school and residencies with

a mandatory internship-year in either Medicine (Internal and/or Pediatrics) or General Surgery.

4. As the M&M Conference is the legally protected, non-discoverable discussion venue under federal law, 38 U.S. Code § 5705, I would recommend that the President of the United States ask of the Secretary of the U.S. Department of Veterans Affairs to convene an M&M conference on the 10th floor of the VACO building across Lafayette Square from *The White House*.[257-259] Such an M&M conference should be purposed to develop an outline throughout U.S. Medicine to better define adherence to Scientific Principles in daily Medical Clinical Practice. Such an M&M conference should include past and present members of the FDA, the NIAID, the NIH, the CDC, the US PHS, the VA (with the VHA USH or his/her designee leading the M&M conference); present and past editors of the *New England Journal of Medicine* and *JAMA*; and Doctors Joyner, Petroski, Casadevall, Henderson, etc. of the FDA/Mayo Clinic CCP protocol, etc. I would recommend a few surgeons be present who are well-versed and committed to the M&M conference—unfortunately, the one's most appropriate in my eyes are all dead: C. Rollins Hanlon, MD, F.A.C.S., Vallee Willman, MD, F.A.C.S., C. Everett Koop, MD, F.A.C.S., J. Eugene Lewis, MD, F.A.C.S., C. Hiram Polk, MD, F.A.C.S., Frank E. Johnson, M.D., F.A.C.S., Claude H. Organ, Jr, MD, F.A.C.S., C. Hiram Polk, M.D., F.A.C.S., etc. While the living surgeon of today might not be as precise and focused as those Surgeon-educator-trailblazers, most assuredly, I could suggest some surgeon-educators whom I know personally that hold the importance of the M&M conference in the highest of regard. The topics to be discussed at such an M&M meeting(s) could come from the 72 index items on pages e-5 and e-6 of *Book 1—Dear Mr. President: COVID-19 and Where We Went Wrong*. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02 https://www.govinfo.gov/content/pkg/USCODE-2023-title38/pdf/USCODE-2023-title38-partIV-chap57-subchapI-sec5705.pdf [37,85,93]

5. While I have subscribed to *The New England Journal of Medicine* (NEJM) [80,98,142,143] over most of my 47 years of medical education and practice and believe in the stated "integrity"[80] of the NEJM, this paper submission may be rejected by the editors of *The New England Journal of Medicine*. Regardless of what the editors of the NEJM decide, I will try to spread the news in whatever method will stimulate public awareness, e.g. uploading to the *Internet Archive*[87-89]; submitting it to the NIAID case #12276 [Attachment IV] for historical preservation within the U.S. Government , the FDA, the CDC, and the VA; writing the President of the United States, mailing it to members of Congress, etc. Personally, I see it as my duty as consistent with my commitment to the *Hippocratic Oath* as a Physician and Surgeon to stimulate the discussions and revisions of our concepts regarding COVID-19 that should follow from the distribution and dissemination of this draft paper wherever possible (even prior its possible publication in NEJM) to, e.g.: Medical Schools, Academia, the pharmaceutical industry, Government Health Agencies, and, figuratively speaking, every mall, every grocery store, every barber shop, and every street corner in America, etc.

On August 16, 2024, the NIH officially removed direct electronic access to the NIH COVID-19 Treatment Guidelines by removing the URL: https://www.covid19treatmentguidelines.nih.gov/ from the Internet. Using the Wayback Machine, one could find that the guidelines were captured by the *Internet Archive* 4,983 times between April 21, 2020 and August 17, 2024: https://web.archive.org/web/20250000000000*/https://www.covid19treatmentguidelines.nih.gov/ As was stated in the *Annals of Internal Medicine* of November 2024[260]:

> Development of treatment guidelines is not a typical role for the U.S. Department of Health and Human Service (HHS) and the National Institutes of Health (NIH); rather, such guidelines are usually developed by professional societies or the Centers for Disease and Prevention (CDC). However, given the NIH's long experience in creating HIV treatment guidelines, HHS requested that the NIH take the lead in expeditiously creating **"living"** treatment guidelines for COVID-19 that would be both widely accessible and frequently updated as important new information became available. This mandate posed special challenges in terms of obtaining sufficient time and attention from experts who were also responsible for their local institutional COVID-19-related clinical activities. Additional challenges included obtaining administrative support for coordinating operations, editing, and website management.
>
> The NIH COVID-19 Treatment Guidelines (the Guidelines) were intended not as a mandate for clinicians or patients but as one source of credible expert advice that would evolve over time as additional data became available to inform therapeutic management strategies. The first release of the Guidelines was on 21 April 2020.
>
> With the declaration of the end of the COVID-19 public health emergency (1,2), the NIH has determined it is now appropriate to sunset the NIH COVID-19 Treatment Guidelines. Drugs approved by the U.S. Food and Drug Administration (FDA) for treatment of COVID-19 are now available; outcomes for patients with COVID-19 are currently much better than in 2020 to 2022; and other organizations, such as the American College of Physicians, the Infectious Disease Society of America, the Pediatric Infectious Diseases Society, the World Health Organization, now provide readily accessible guidelines of their own (3-6).
>
> The last update to the Guidelines (Supplement 1, available at Annals.org) was posted on 29 February 2024. All of the archived versions of the Guidelines from April 2020 to the last release are available at https://wayback.archive-it.org/4887/20240626155844/https://www.covid19treatmentguidelines.nih.gov ***[https://www.covid19treatmentguidelines.nih.gov can thus only be found today through the Wayback Machine of the Internet Archive.]***

For all of history, the U.S. National Institutes of Health (NIH) has figuratively, circuitously, electronically **discontinued the path to** their contributions to the guidelines they advanced during the American COVID-19 epidemic which, at the time, they claimed were "… 'living' treatment guidelines for COVID-19." **Shame on the NIH** and shame on us all! I would allege, the NIH represents, in this case all of U.S. Medicine which essentially destroyed (or at least obfuscated) for all of history: the knowledge, the logic, the therapeutic intent, etc.--truths and errors--that were functionally driving our addressing of the American epidemic caused by the coronavirus, SARS-Cov-2, COVID-19, that confronted the people of the United States of America from 2020 to the present day--and, is still endemically, ongoing!

Over the four-year interval to the last publication of the *NIH COVID-19 Treatment Guidelines* of February 29, 2024 (and subsequent discontinuation of the URL by the NIH on https://www.covid19treatmentguidelines.nih.gov of August 16, 2024[260]):

> The Guidelines consisted of 90 pages in the first iteration, 278 pages at the end of 12 months, and 478 pages in the last edition. Forty pages were archived when their contents were deemed to no longer be

> relevant for clinicians. From 21 April 2020 until the final update on 29 February 2024, the Panel voted on recommendations 438 times (Table 5 of **Supplement 2**).
>
> In total, there were 71 updates of the Guidelines from April 2020 through February 2024. As shown in **Figure 1**, updates, rapid communications, and revisions were initially frequent and then slowed in 2023 and 2024. These were generally driven by the release of data from clinical trials, information from other publications that was important to therapeutic management, or announcements from the FDA.
>
> From the beginning of the pandemic through February 2024, the FDA issued 17 emergency use authorizations (EUAs) for COVID-19-related drugs. Of these 17 17 EUAs, 4 of the drugs (hydroxycholoroquine, COVID-19 convalescent plasma, anakinra, and vilobelimab) were not recommended for use by the Panel. **Figure 2** shows the timing of FDA actions for preventive and therapeutic products related to management of COVID-19 from March 2020 to February 2024.
>
> As of 29 February 2024, the Guidelines had received more than 50 million page views from more than 26 million users. The number of unique users (**Figure 3**) and page views closely followed the curve of pandemic hospitalizations in the United States. Unpredictable surges in caseloads highlighted the importance of keeping the recommendations current. Although most page views were from the United States, approximately 20% to 25% were from other countries, notably Australia, Canada, India, Japan, Malaysia, Mexico, and Thailand.

The sunsetting by electronic overwriting and paltering iterations of *NIH COVID-19 Treatment Guideline* [260] has been tantamount to the destruction of the 72 URLs of the *NIH COVID-19 Treatment Guidelines* akin to a Nazi book burning[261] but stealthily in American society today. Such electronic sunsetting may be dutifully an electronic preservation of all 72 iterations on the computerized server farm of the *Internet Archive*--a non-governmental, non-profit 501(c)(3) institution[87-89]; but in reality, though, the electronic sunsetting of medical history is subtly obfuscative; intricately, minimally discoverable; and surreptitiously destructive of human knowledge. I would allege that as the NIH is an agency of the U.S. Department of Health and Human Services (DHHS), the electronic sunsetting of the *NIH COVID-19 Treatment Guidelines* is a violation of the intent of the Sarbanes-Oxley Act of 2002, 18 U.S.C. §15129(c)(1).[103] Such electronic-storage-only is unintellectually and unethically suppressive by the *de facto* failure to the preserve tangibly in an accessible hardcopy format for future generations the trials and tribulations and accomplishments and mistakes in our society's most-recent attempts at the advancement of human knowledge regarding COVID-19. Instead of disguising the 72 iterations of the NIH COVID-19 Treatment Guidelines[260] from future medical practitioners, every hospital and medical school library in the U.S.A. should printout all 72 iterations and shelve them as a medical series physically in their tangible Reference sections, e.g.: Using a computer and a color laser printer, one can printout each iteration from the *Internet Archive*[87-89] for inclusion in such a medical reference series with just a half-a-ream of paper, 4 printer cartridges, binding materials, and approximately 15 minutes of computer printer time and human effort (72 iterations x ¼ hour = 18 man-hours /library).—that, to me, seems like a bargain in the preservation of the present medical thought process for all of history.

So, as coronavirus, SARS-Cov-2, COVID-19 is an endemically ongoing scourge of man, why have we electronically misplaced the 72 interactions—correct or incorrect--of the NIH COVID-19 Treatment Guidelines? All of us in U.S. Medicine have the ethical responsibility to sort out the truth in Medicine. We are ethically mandated by our profession to explain to the American people in a clear and concise manner the applicability of the medical doctrine in their individual daily lives and individual medical care. Early-on in the American COVID-19 epidemic, this was pointed out to the American people--so *apropos* on April 1, 2020, April Fools' Day--in an interview of Dr. Fauci by Norah O'Donnell on the CBS Nightly News[262]:

> Norah O'Donnell: With all due respect it does seem like so much of this we're making it up as we go along.
>
> Dr. Anthony Fauci: Well, you know you make it up as you go along, Norah, because that's what you know—that's where the war is all about. I don't like to necessarily make that analogy to a war, but if you talk to the generals with experience, you have a plan. But when the bullets start flying, everything becomes a fog, and you have to play it by ear. We do have a good plan. We need to be humble that we don't know all the answers, and we don't know how exactly this is going to turn out.
>
> Norah O'Donnell: Dr. Fauci, thank you so very much for your time and expertise.
>
> Dr. Anthony Fauci: It's always good to be with you, Norah. Thank you.

O'Donnell N: BREAKING NEWS: Dr. Fauci on the fight against the virus. https://www.facebook.com/CBSEveningNews/videos/norah-odonnell-should-we-be-advising-people-to-wear-masksdr-anthony-fauci-great-/204826050813336/ 2020 April 1, 2:10 – 2:48

In the fight against the American COVID-19 epidemic, as physicians and surgeons of U.S. Medicine, did we really live up to Francis W. Peabody's admonition 100 years ago emphasizing our basic underlying moral promise to humanity as individual physicians towards each and every unique, individual patient that presents to us?--For:

"…the secret of the care of the patient is in caring for the patient."[255,256]

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Licensed Physician and Surgeon (MO [R8A85], IL [036.093146], CA [G86301]), American Board of Surgery certified General Surgeon [32104], Member of the AMA [ME# 02834790044] and Fellow of the American College of Surgeons [03009583]
Retired, Physician and Surgeon, Veterans Health Administration, U.S. Department of Veterans Affairs
Retired, Physician, Surgeon, Physician-Scientist, and tenured Professor, Department of Surgery, Saint Louis University School of Medicine

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1.) Nobody defined the foundational basics of Clinical Immunology: Active Immunization and Passive Immunization.
2.) Everything was in Generalities – NOT THE INDIVIDUAL PATIENT!

3.) The not-for-profit American Red Cross was *NOT* officially invited "to the table" until July 30, 2020—by that time, the U.S.A. had gone so far down the Rabbit Hole, they did not know how to get out!

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> Antibodies have been used for a century for the prevention and treatment of infectious diseases (Table 1). In bacterial disease, antibodies neutralize toxins, facilitate opsonization, and, with complement, promote bacteriolysis; in viral disease, antibodies block viral entry into uninfected cells, promote antibody-directed cell-mediated cytotoxicity by natural killer cells, and neutralize virus alone or with the participation of complement.
>
> Prior to the use of antibiotics, antibodies were the only specific agents for the treatment of certain infections. Although this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1). Since several excellent reviews are available, this article will emphasize new developments (30, 31, 101, 164, 165).
>
> Antibodies can be administered as human or animal plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or convalescing donors, and as monoclonal antibodies (Mab) (30, 164,178). The therapeutic use of Mab is increasing dramatically, but only one (palivizumab for respiratory syncytial virus [RSV]) has been licensed for prophylaxis of an infectious disease.

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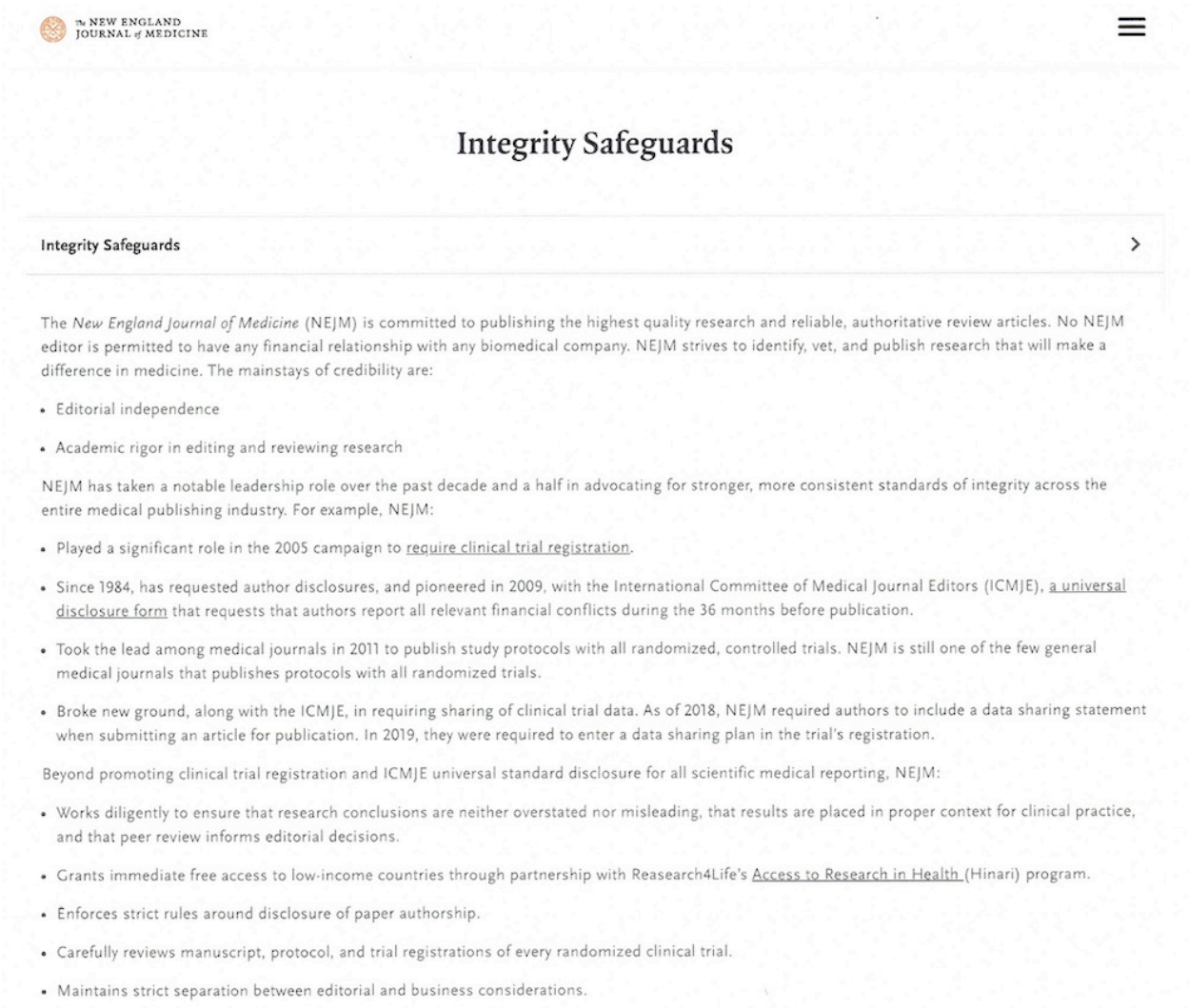

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> **5. RECISSIONS.** VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005 is rescinded……. (page 1). [***Please note that when one searches for VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005, one is redirected to VHA Handbook 1400.01. Using the Wayback Machine and the previous URL for VHA 1400: http://web.archive.org/web/20161221045318/https://www.va.gov/oaa/1400_1hk_Oct2001.doc , one can find the 2001 version in the 2004 of the Internet Archive captures. There are no other captures of this URL in the Wayback Machine except December 21, 2016 which brings up the VA Website which states: "Page Not Found."***
>
> **4. Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and able to provide direct supervision or consultation without delay as needed. (page 9)

116. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063, Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. The original version of VHA Directive 1063 of December 24, 2013 which claimed physician assistants could be independent practitioners --which I would allege is a violation of every State Medical Boards' credentialling policies/laws regarding Physician Assistants. In the 2013 version, the justification of the violation of all State Medical Boards was in 2.c:

Under the Supremacy Clause of the U.S. Constitution, States are prohibited from regulating or controlling the activities of the Federal Government without written Congressional consent; where Federal and State laws conflict, Federal law governs official actions of Federal employees. Examples of the types of activities that the Federal Government may establish are qualifications for employment and scopes of practice. Therefore, the establishment of scopes of practice for VA PAs defined by this Directive is without regard to State Practice Acts.
https://web.archive.org/web/20140814150238/https:/www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958

117. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063 (1), Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. Captured on July 22, 2023, by the *Internet Archive.* https://web.archive.org/web/20230722070741/https://www.va.gov/VHAPUBLICATIONS/ViewPublication.asp?pub_ID=2958 In **2. SUMMARY OF CHANGES** of the **Transmittal Sheet** which is still labelled **December 24, 2013** but in red has stamped: **AMENDED May 17, 2022** is: (1) Paragraphs 2.c. and 2.e. removes references to the Supremacy Clause reference and physician liability.—which means that the independent practice of a VHA Physician Assistant was rescinded returning all Physicians Assistants to the State Medical Board statutes outlining mandatory Physician scope of practice affiliations and legally mandated Physician oversight. The signatory official on this document is Robert A. Petzel, M.D., Under Secretary for Health who had been terminated over the Phoenix VAMC scandal 8 years prior to this as noted above in references 36 and 37.

118. Petzel RA: Utilization of Physician Assistants (PA) VHA Directive 1063(2), December 24, 2013 AMENDED June 24, 2024. When one uses a search engine like GOOGLE or enters the official URL of this document site: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 , one is electronically shifted to a .pdf file, e.g.: file:///Users/andrusmd1/Downloads/1063(2)_D_2013-12-24%20(6).pdf. The https://... URL version was captured by the *Internet Archive* on July 18, 2024. The signatory official on this document is still Robert A. Petzel, M.D., Under Secretary for Health, who had been terminated over the Phoenix VAMC scandal 10 years prior to this as noted above in references 36 and 37. https://web.archive.org/web/20240718212213/https://www.va.gov/VHApublications/ViewPublication.asp?pub_ID=2958

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After OIG Inspector Griffin's testimony on May 8, 2003, ABC *Primetime* investigated for an entire year and on April 8, 2004, aired Fighting for Care narrated by Diane Sawyer. 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212) This episode was removed from the ABC Archives possibly because ABC to hidden cameras into the Cleveland and Temple, TX VAMCs. 2004 George Polk Award for "**Television Reporting: Diane Sawyer** and **Robbie Gordon**, ***ABC News PrimeTime Live***, for **"Fighting for Care,"** which documented patient abuse and deplorable conditions in VA hospitals." (for investigative reporting excellence) https://liu.edu/polk-awards/past-winners#2004. When Tammy Shehari, the Associate Producer for the episode, spoke with me by phone in 3/2004, she asked me to estimate how many additional veterans had died due to unsupervised operations performed by Surgery Residents– I declined to guess because to do so would be wrong and a disservice to the Veteran patients and the men and women of Department of Veterans Affairs that do their duty faithfully for Veteran patients. (The interview ended shortly after my refusing to guess, and this was the only time ABC News spoke with me.)

Please note the reference above -- VHA USH, Robert Roswell, M.D. resigned three days prior to the airing of *Fighting for Care*. *Fighting for Care* contained within unauthorized hidden cameras in the Cleveland VAMC and the Temple TX VAMC. The VA spin was: …Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. …. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

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> …Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging…

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> Pages 1 – 2:
>
> On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)[3] for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)4 , pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.
>
> On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers has been revised to provide updated clinical trial results and supporting data.[5] ***(VERY IMPORTANT: This negative statement: "…by no longer limiting its use to the treatment of patients with severe disease…" is obfuscation by the FDA.*** ***The positive statement that the FDA failed to state at the time and FDA has never stated is: Veklury (Remdesivir) is indicated most efficaciously in the early treatment of COVID-***

19 in the viremic phase (best within 72 hours of diagnosis) because it inhibits RNA polymerase replication of the COVID-19 RNA. The justifying REASON for this is: "The active form of remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2. Remdesiviris incorporated by the RdRp into the growing RNA product and allows for addition of three more nucleotides before RNA synthesis stalls. …" *Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Hobartner C, Cramer P: Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nature Communicatioins (2021)12:279* https//doi.org/10.1038/s41467-020-20542-0 https://www.nature.com/articles/s41467-020-20542-0.pdf

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360 bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] The May 1, 2020 EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to add references to remdesivir's trade name, "Veklury." "Veklury" is used in this August 28, 2020 reissued letter.

[4] For purposes of the May 1, 2020 EUA, patients with severe disease were defined as patients with oxygen saturation ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

[5] Prior to this reissuance and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration

Pages 2-3:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

Distribution of the authorized Veklury will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA

> Gilead will supply Veklury to authorized distributors[7] , or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and

The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

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SAFETY OUTCOMES

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group (Table S17). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients) (Table S19). No deaths were considered by the investigators to be related to treatment assignment.

Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group (Table S18); 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo (Table S17). The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level (Table S20). The incidence of these adverse events was generally similar in the remdesivir and placebo groups.

Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratory-confirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3). A variety of therapeutic approaches including novel antivirals, modifiers of the immune response or other intrinsic pathways, and combination approaches are needed to continue to improve outcomes in patients with Covid-19.

156. Farley JJ, Director, Office of Infectious Diseases, U.S. Food & Drug Administration: FDA New Drug Approval for Remdesivir **NDA 214787**. Letter from John Farley, MD, MPH to Ms Rhoades, Gilead Sciences, Inc. authorizing a **New Drug Authorization Approval** 2020 October 22

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf

NDA APPROVAL 214787

Gilead Sciences, Inc.
Attention: Ashley Rhoades, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Rhoades:
Please refer to your new drug application (NDA) dated and received August 7, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEKLURY (remdesivir) injection, 5 mg/mL; VEKLURY (remdesivir) for injection, 100 mg/vial.

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) **for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.**

157. Rubin D, Chan-Tack K, Farley J, Sherwat A: FDA approval of remdesivir—A step in the right direction. N Engl J Med 2020 December 31; 383: 2598-2600. https://www.nejm.org/doi/pdf/10.1056/NEJMp2032369

158. Downs Burger J: Novel coronavirus: EMTALA compliance for hospitals with dedicated emergency departments. Arnall, Golden, Gregory LLP 2020 March 09 https://www.agg.com/news-insights/publications/novel-coronavirus-emtala-compliance-for-hospitals-with-dedicated-emergency-departments-2/

159. Azar AM: Waiver or modification of requirements under section 1135 of the Social Security Act. 2020 March 13. www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx previous has been taken off the web; therefore using the Wayback Machine, there are 162 captures of which this is the March 16, 2020 capture: https://web.archive.org/web/20200316224950/www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx

160. Bruce JM, Mitchell JO: HHS waives certain EMTALA requirements, Medicare conditions of participation, and HIPPA sanctions during the COVID-19 Pandemic. The National Law Review 2022 March 25; XII (84): 1-7. https://www.natlawreview.com/article/hhs-waives-certain-emtala-requirements-medicare-conditions-participation-and-hipaa

161. ACEP COVID-19 Field Guide: EMTALA Regulations and Liability. https://www.acep.org/corona/covid-19-field-guide/regulations-and-liability/emtala/

which can no longer be found on the Internet but using the Wayback Machine, 20 captures are noted with the first capture being August 6, 2020. https://web.archive.org/web/20200806015843/https://www.acep.org/corona/covid-19-field-guide/regulations-and-liability/emtala/

162. President Trump signed into law PL-115-176: Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina, the RIGHT TO TRY ACT OF 2017. 2018 May 30 https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf

163. Agarwal R, Saltz LB: Understanding the Right to Try Act. Clin Cancer Res. 2020 Jan 15; 26(2): 340-343. (HHS Public Access Author manuscript, Clin Cancer Res. Author manuscript; available in PMC 2020 August 10. Nihms-1541631.pdf https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7416898/). https://pmc.ncbi.nlm.nih.gov/articles/PMC7416898/pdf/nihms-1541631.pdf

164. Trump D: Donald Trump August 23 White House COVID-19 Press Conference Transcript. Rev Aug 23, 2020. Video of the conference: https://www.youtube.com/watch?v=nE0EkrElCRk Transcript: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript which can no longer be found on the Internet but using the Wayback Machine, 12 captures are noted with the first capture being September 1, 2020.

165. Andrus CH: Re: Thousands of Americans are *needless dying* because the FDA is illegally ignoring PL 115-176 – The *Right to Try Law* and COVID-19 Convalescent Plasma has NOT been given as Prophylaxis and Early after COVID-19 positivity conversion**. Letter mailed to President Trump and the offices of the U.S. Senate.**
0.8 Attachment VII Letters to Members of Congress and Pres Trump 8_23_2020 and 8_28_2020

https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02/page/993/mode/1up?q=Members+of+Congress&view=theater

166. FDA News Release: FDA issues emergency use authorization for Convalescent Plasma as potential promising COVID-19 treatment, another achievement in Administration's fight against pandemic. U.S. Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

> Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency's ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.
>
> Today's action follows the FDA's extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.
> The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:
"The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Secretary Azar. "The Trump Administration recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private partners began work on making this product available across the country while continuing to evaluate data through clinical trials. Our work on convalescent plasma has delivered broader access to the product than is available in any other country and reached more than 70,000 American patients so far. We are deeply grateful to Americans who have already donated and encourage individuals who have recovered from COVID-19 to consider donating convalescent plasma."

Stephen M. Hahn, M.D., FDA Commissioner:
"I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as possible in order to save lives. We're encouraged by the early promising data that we've seen about convalescent plasma. The data from studies conducted this year shows that plasma from patients who've recovered from COVID-19 has the potential to help treat those who are suffering from the effects of getting this terrible virus," said Dr. Hahn. "At the same time, we will continue to work with researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent plasma in treating patients infected with the novel coronavirus."

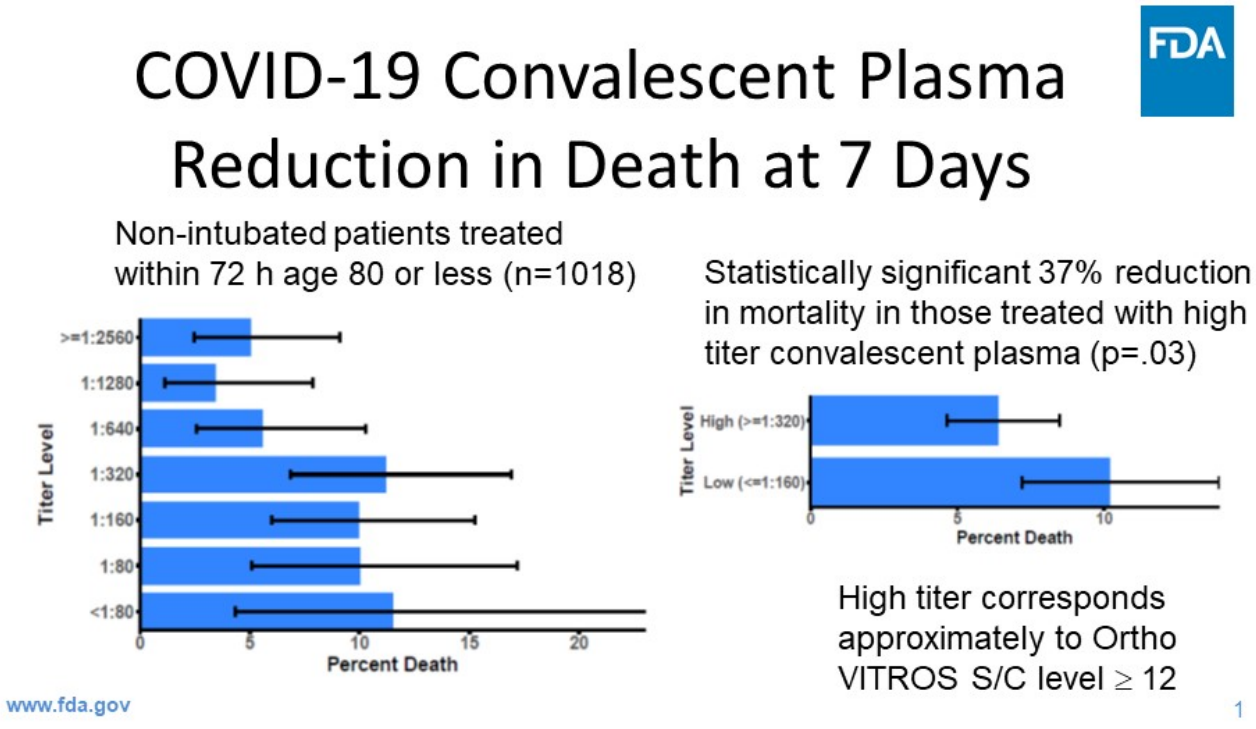
Scientific Evidence on Convalescent Plasma

Based on an evaluation of the EUA criteria and the totality of the available scientific evidence, the FDA's Center for Biologics Evaluation and Research determined that the statutory criteria for issuing an EUA criteria were met.

The FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that that there are no adequate, approved, and available alternative treatments.

The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of patients into any of the ongoing randomized clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet represent a new standard of care based on the current available evidence.

The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.



The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products

167. FDA: Updated Evidence to Support the Emergency Use of COVID-19 Convalescent Plasma – as of 9/23/2020. https://www.fda.gov/media/142386/download

Table 1. 7- and 28-Day Deaths in Patients Treated with COVID-19 Convalescent Plasma

	7-day			28-day		
	Overall (N=4330)	Not Intub (N=2488)	Not intub, ≤80 y, ≤72 h (N=932)	Overall (N=2817)	Not Intub (N=1238)	Not intub, ≤80 y, ≤72 h (N=485)
Deaths Lower Titer	14.97%	13.99%	11.29%	49.57%	49.43%	46.63%
Deaths Higher Titer	13.61%	11.00%	6.27%	46.21%	41.48%	33.23%
Absolute Improvement	1.36%	2.99%	5.02%	3.36%	7.95%	13.40%
Relative Improvement	9%	21%	44%	7%	16%	29%
Statistical Significance	Not significant	Significant p=0.03	Significant p=0.008	Not significant	Significant p=0.004	Significant p=0.004

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171. 2020-07-07 Casadevall A, Joyner MJ, Pirofski LA: SARS-CoV-2 viral load and antibody responses: the case for convalescent plasma therapy. J Clinical Investigation 2020 Jul 7; 130 (10): 5112-5114. https://www.jci.org/articles/view/139760/pdf

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Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimabal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Soto JCD, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS. COVID-19 Convalescent Plasma in 20,000 hospitalized patients. Mayo Clin Proc September 2020; 95(9): 1888-1897. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7368917/pdf/main.pdf

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176. 2021-05 Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, Grossman BJ, Henderson JP, Musser J, Salazar E, Hartman WR, Bouvier NM, Liu STH, Pirofski LA, Baker SE, van Helmond N, Wright TS, Fairweather D, Bruno KA, Wang Z, Paneth NS, Casadevall A, Joyner M: The effect of convalescent plasma therapy on COVID-19 patient mortality: Systematic review and meta-analysis. Mayo Clin Proc, 2021 May; 96 (5): 1262-1275. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7888247/pdf/main.pdf

> … Importantly, many of the patients enrolled in the studies included in the analyses received convalescent plasma transfusions later in their disease course. In this context, before antibiotics and effective vaccinations, convalescent plasma therapy was widely understood to be most efficacious very early in the course of hospitalizations.[2, 155] As a result, our analysis may underestimate the mortality reduction achievable through early administration of high-titer convalescent plasma for COVID-19.
>
> **Conclusion**
> This real-time systematic review and meta-analysis of contemporaneous studies highlights that the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19 and suggests that **early transfusion of high-titer plasma represents the optimal use scenario to reduce the risk of mortality among patients with COVID-19**. These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent.

177. 2021-06-04 Casadevall A, Dragotakes Q, Johnson PW, Senefeld JW, Klassen SA, Wright RS, Joyner MJ, Paneth N, Carter RE: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. eLife 2021; 10e69866. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205484/pdf/elife-69866.pdf

> **Abstract:** ***(Extremely Important!)***
> …Changes in the number of hospital admissions, SARS-CoV-2 variants, and age of patients could not explain these findings. The retreat from CCP might have resulted in as many as 29,000 excess deaths from mid-November 2020 to February 2021.
> **Conclusions:** A strong inverse correlation between CCP use and mortality per admission in the USA provides population-level evidence consistent with the notion that CCP reduces mortality in COVID-19 and suggests that the recent decline in usage could have resulted in excess deaths.

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180. 2022-03-07 Casadevall A, Grossman BJ, Joyner MJ, Henderson JP, Paneth N, Pirofski LA, Shoham S: National COVID-19 Convalescent Plasma Project. Last digitized for International Archive, March 7, 2022.

https://ccpp19.org/about/index.html which can no longer be found on the Internet but using the Wayback Machine, 152 captures are noted with the first capture being April 1, 2020.

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182. Villa CH, Medical Officer, OBRR/DBCD/CRS, U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210226104738/https://www.fda.gov/media/141480/download

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185. Wikipedia: Michaelis-Menten kinetics. https://en.wikipedia.org/wiki/Michaelis-Menten_kinetics

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inflammatory damage in COVID-19. Proceedings of the National Academy of Sciences. 2020-June 20 https://www.pnas.org/content/117/23/12529

> First of all, this study was a pilot trial and the aim was to investigate the safety of CP transfusion, which was defined as the primary endpoint (3). We nevertheless also explored the possible therapeutic benefits of CP by examining its effectiveness in neutralizing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in ameliorating clinical symptoms and paraclinical criteria in recipients. Indeed, the adverse effect was minor, whereas a quickly improved outcome of 10 severe COVID-19 patients was observed. There are of course a number of issues to be addressed, such as the confirmation of the clinical effectiveness in a phase II controlled, randomized trial.
>
> Second, the objective for CP transfusion in severe COVID-19 therapy is based on an in-depth understanding of disease mechanisms. The pathogenesis of this epidemic involves the interaction between viral replication of SARS-CoV-2 and human immune response (4). Particularly, in severe or critical COVID-19 cases, lung alveolar macrophages or epithelial cells could produce various proinflammatory cytokines and chemokines, which recruit monocytes and neutrophils to the infection site to clear the virus particles and infected cells, resulting in uncontrolled inflammation. The uncontrolled virus infection leads to more macrophage infiltration and a further worsening of lung injury. Therefore, the key point of CP therapy is to neutralize the virus and to interrupt the vicious cycle of excessive activation of the immune response in severe patients. In our study, 200 mL CP containing neutralized antibody above 1:640 rapidly cleared the viremia and achieved clinical improvement. Considering the accessibility of plasma donors, using CP as replacement fluid for the therapeutic plasma exchange may be not feasible.
>
> Third, the optimal treatment time and dose of CP need to be determined by the knowledge on viral proliferative kinetics. Zhou et al. (5) reported that the median viral shedding time was 20.0 d in survival patients. Huang et al. (6) observed that the viral load gradually decreased in the respiratory tract after 7 d of illness onset but can be detected after 28 d of illness onset in two-thirds of critically ill patients. Chen et al. (7) found the serum viremia was detected in 29.4% (5/17) critically ill patients and was significantly correlated with the level of interleukin-6. Thus, monitoring the dynamic changes of interleukin-6 level, which was significantly elevated in COVID-19, may help to determine the optimal treatment time, generally within 2 wk.
>
> Finally, the optimal time for collecting CP should be determined by the time and level of total antibody production in convalescent patients. The presence of antibodies was <40% among patients within 1 wk since onset and rapidly increased to 100.0% (antibody), 94.3% (immunoglobulin M), and 79.8% (immunoglobulin G [IgG]) since day 15 after onset (8). Also, the neutralizing antibody titer was correlated with the IgG antibodies (9). The median duration of hospitalization for COVID-19 patients was 12.0 d (**10**). In our study, all of the donors were recovered from the common type of COVID-19. Therefore, the collection of CP from the convalescent patients may be 3 wk after the illness onset, and routine inactivation of plasma should be performed for elimination of potential existing virus. The optimal dose of CP can be calculated based on an empirical formula: volume (liters) = weight of the recipient (kilograms) × the antibody titer of CP.

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Abstract Results Convalescent plasma recipients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% Cl: 0.75~0.98; p=0.028). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p = 0.039). In a covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% Cl: 0.05~0.72); p = 0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752).

Mr. President: What the abstract results above mean is that if the patients require intubation (at the end of the Cytokine Cascade and Bradykinin Storm), then there was no survival advantage to *Passive Immunization* with COVID-19 Convalescent Plasma.--***BUT,*** if COVID-19 Convalescent Plasma was given before intubation, in all analyses in this study, there was a significant survival advantage (i.e.: all p values were < 0.05).

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a world-wide pandemic with overwhelming socioeconomic impact. Since inflammation is one of the major causes of COVID-19 complications, the associated molecular mechanisms have been the focus of many studies to better understand this disease and develop improved treatments for patients contracting SARS-CoV-2. Among these, strong emphasis has been placed on pro-inflammatory cytokines, associating severity of COVID-19 with so-called "cytokine storm." More recently, peptide bradykinin, its dysregulated signaling or "bradykinin storm," has emerged as a primary mechanism to explain COVID-19-related complications. Unfortunately, this important development may not fully capture the main molecular players that underlie the disease severity. To this end, in this focused review, several

lines of evidence are provided to suggest that in addition to bradykinin, two closely related vasoactive peptides, substance P and neurotensin, are also likely to drive microvascular permeability and inflammation, and be responsible for development of COVID-19 pathology. Furthermore, based on published experimental observations, it is postulated that in addition to ACE and neprilysin, peptidase neurolysin (Nln) is also likely to contribute to accumulation of bradykinin, substance P and neurotensin, and progression of the disease. In conclusion, it is proposed that "vasoactive peptide storm" may underlie severity of COVID-19 and that simultaneous inhibition of all three peptidergic systems could be therapeutically more advantageous rather than modulation of any single mechanism alone.

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196. Andrus CH: Thank you letter to Gilead Sciences for providing the reference regarding the date of completion of Phase 1 remdesivir trial. 2022 February 16

From: Charles.Andrus@va.gov,
To: Public_affairs@gilead.com,
Cc: Charles.Andrus@va.gov, candrus600@aol.com, Anthony.Fauci@nih.hhs.gov, kara.harris@nih.hhs.gov, Janet.Woodcock@fda.hhs.gov, Denise.Hinton@hhs.gov, Jacqueline.OShaughnessy@fda.hhs.gov, michael.hogan@va.gov,
Subject: RE: Phase 1 remdesivir trial result
Date: Wed, Feb 16, 2022 3:25 pm
Attachments: 3 Andrus SLU cv 8_11_2021.docx (7964K),

2/16/2022

NIAID Case #12276

Dear Gilead:

Thank you for forwarding this article to me: Humeniuk R, Mathias A, Huyen C, Osinusi A, Shen G, Chng E, Ling J, Wu A, German P: Safety, Tolerability, and Tolerability, and Pharmacokinetic of Remdesivir, An antiviral for Treatment of COVID-19, in Healthy Subjects. Clin Transl Sci 2020; 13, 896-906: Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID 19, in Healthy Subjects (wiley.com). I have attached a copy of my CV so you know who I am. Over my decades of involvement with the Veterans Health Administration (VHA), U.S. Department of Veterans, I have attempted to be an advocate for each and every individual Veteran patient that presented to me. My biggest challenge was to have the phrase in VHA Handbook 1400.1 on Resident Supervision revised (after ~50 years): **Level 3: Attending Surgeon not present, immediately available.** What was condoned by the inappropriate application of Level 3 was that on nights, weekends, holidays, family get togethers, etc., some University Attending Surgeons would staff residents in the OR from afar (ghost surgery). Twenty years ago, I fought for that change all the way to the U.S. Court of Appeals for the Federal Circuit in *Andrus v VA*, Case 03-3162—in which the court *per curium* "failed to rule." I lost all my battles with the VA; but, in the end, all Attending Surgeons-of-Record in the VA today are required to be present in the OR suite during every individual Veterans' operation which is definitely to the betterment of every Veteran patient. The VA saved face by: 1.) changing VAH Handbook from 1400.1 to VAH Handbook 1400.01 so you can't find previous versions electronically if you don't know the previous URL.; 2.) as is common practice today, in the agencies of the Executive Branch of the Federal Government, electronically overwrite documents

without designating what has been rescinded or that there was even a previous document; and 3.) I became and still am an *unperson* in the VA from 4/1982-8/2016 since my Official Personnel File (OPF) has been misplaced/lost. Thus, from April 1982 to August 2016, I don't exist in the VA until I returned in August 2016, as an Attending Physician and General Surgeon at the St. Louis VAMC. My VA service from 1982 to 2002 does not exist "officially" even though from 8/1996 to 1/2002, I was the Chief of Surgery, Edward Hines, Jr. VAH (the first hospital of the University-VA affiliation in 1946 under PL-79-293); and I was interviewed for the position of Under Secretary for Health

(USH) of the Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (DVA) on the 10th floor of VACO (across Lafyette Square from *The White House*) on the afternoon of December 10, 1999. I am telling you this, so I can put in context for you the convoluted process regarding Remdesivir that parallels that which occurred to me in my fight to stop Physically Unsupervised resident surgeons by VA misdirection and obfuscation twenty years ago. Today, by changing URLs, electronic overwriting, and semantics, the FDA, the NIH, the CDC, the VA, etc. have somewhat stretched the truth before the American people.

I thank you for forwarding the reference regarding the Phase I studies completed for Remdesivir (RDV). As is quoted in the article:

On May 1, 2020, based on available data from to global clinical trials, the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-

19[19,22,23] Based on these clinical data, RDV has been approved for the treatment of adults and pediatric patients in

Japan.[24] This paper describes the safety and pharmacokinetics (PKs) of the solution and lyophilized formulations of i.v. RDV administered to healthy participants in the two first-in-human (FIH) phase I studies.

The above paragraph suggests that the FDA issued the EUA after review of the two first-in-human phase I studies involving Remdesivir (VEKLURY) and that review occurred at least by May 1, 2020, which means that phase I human trials were deemed safe and implies that the phase I trials *de facto* were completed—BUT, that presented multiple ethical and legal dilemmas for the FDA, the NIH, etc.

1. The FDA issued the first Remdesivir EUA on May 1, 2020 (which was the date when Dr. Fauci announced Remdesivir from the Oval Office); yet by making it an EUA, Remdesivir,-- the FDA was defining Remdesivir as an "unapproved" drug in the treatment of COVID-19

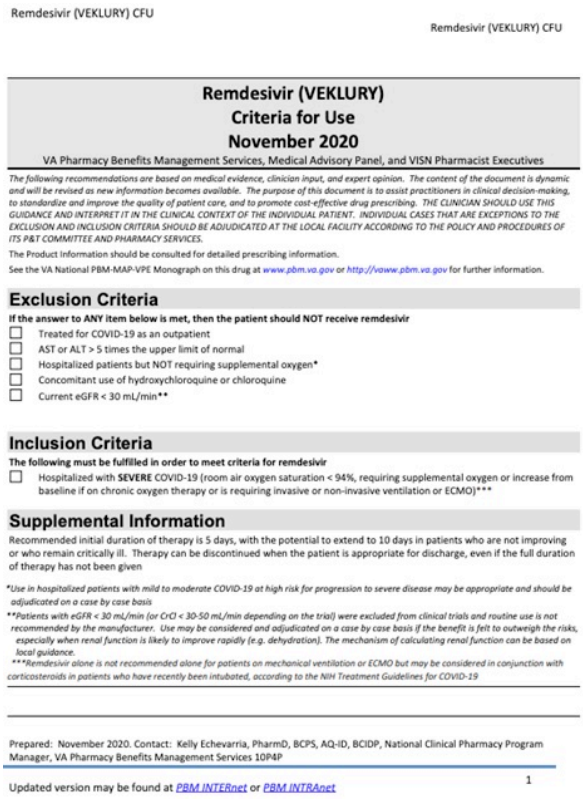
2. As phase II/III clinical trials proceeded, prospective participants who had contracted COVID-19 should have been made aware in their Informed Consent that with The Right to Try Act, PL-115-176 that they could still be afforded Remdesivir by non-participation in the mandated RCT placebo trials—for that matter, all of America should have been told of this by the FDA! As the Phase I studies *de facto* were completed, any American could have asked for Remdesivir under PL-115-176 and should have received it!

3. As I am sure that you are well-aware that Remdesivir is "a single diastereomeric monophoramidate prodrug that inhibits viral RNA polymerases" which works best during the initial

viremic phase of COVID-19—rather than in the later severe disease phases of cytokine cascade and bradykinin storm. Unfortunately, with the issuance of the EUA on May 1, 2020, "the US Food and Drug Administration **(FDA) granted emergency use authorization** to allow RDV to treat adults and children **hospitalized with severe COVID-19**[19,22,23]." In fact, the **FDA removed the severity stipulation quietly**--not notifying the American public of this significant retraction--on **August 28, 2020**. In the FDA January 21, 2022 letter to Madelyn Low, MBS, Manager, Regulatory Affairs, Gilead Sciences, Inc., https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fda-authorization-letter.pdf?la=en&hash=FD3737583BE0E4DF710ADB36AEAA2DBD, there are 8 references on pages 1 and 2 in which the Acting Chief Scientist of FDA outlined the chronology regarding Remdesivir including the August 28, 2020 retraction of the severity of illness stipulation: "...FDA revised authorized use of Veklury to no longer limit its use for the treatment of patients with severe disease." (How could Remdesivir being an "unapproved" drug in the treatment of COVID-19 under the FDA's EUAs standards become a drug that the FDA was officially revising authorization so it could be given early in the course of the disease? It seems like a bunch of semantics; but if that bunch of semantics limits the rights of individuals in America, that is wrong.

4. "On October 22, 2020, FDA also approved NDA 214787 for Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 Kg) **requiring hospitalization."** At this point, Remdesivir (VEKLURY) was designated by the FDA as a prescription drug (NDA 214787) on October 22, 2020.

5. In November 2020, the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs issued for the fully-FDA- authorized-prescription drug, VEKLURY, NDA 214787 the: "Remdesivir (VEKLURY) Criteria for Use" of how to administer Remdesivir with the severity Inclusion Criteria exclusively included that had been removed previously on August 28, 2020 by the FDA:



Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY)
Criteria for Use
November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive remdesivir

- ☐ Treated for COVID-19 as an outpatient
- ☐ AST or ALT > 5 times the upper limit of normal
- ☐ Hospitalized patients but NOT requiring supplemental oxygen*
- ☐ Concomitant use of hydroxychloroquine or chloroquine
- ☐ Current eGFR < 30 mL/min**

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

- ☐ Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

Supplemental Information

Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given

**Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis*

***Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.*

****Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19*

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

Updated version may be found at PBM INTERnet or PBM INTRAnet

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6. When I had a patient denied Remdesivir by the Infectious Diseases service quoting the November VA directive, I contacted Richard Stone, M.D., VHA Chief Medical Executive (the Trump Administration's title for the Under Secretary for Health, VHA, DVA). Dr. Stone contacted VA Pharmacy Management Services and the Medical Advisory Board. At first, the VA responded to me. But when the VA became evasive, I contacted the FDA, the NIAID (Case #12276), and wrote a letter to the editors of the *The New England Journal of Medicine*. None responded to me.

7. I recently had a patient admitted to the Surgical Service who had newly turned COVID-19 positive (less than 24 hours from negative to positive). The recommendations from the same Infectious Diseases service was that if the patient had any symptomatology like headache or neck pain, give three days of Remdesivir; and if the patient develops a cough, give five days of Remdesivir and dexamethasone. By the time of that consult, the CDC had stated a month before that Regeneron's and Eli Lilly's monoclonal cocktails were ineffective against COVID-19, omicron variant; and, thus, GlaxoSmithKline's *sotrovimab* was and is being *de facto* rationed at present time.

Once again, I thank all involved in addressing my question at Gilead regarding if a phase I study had been completed in the case of Remdesivir. You were all very professional and willing to listen—and, most of all, my personal thanks as a Federal Physician and Surgeon for you have provided this information which may become an outstanding service for the people of the United States of America.

Thank you,
Charles Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine

Chief and Attending General Surgeon, Unit II (SLU) General Surgery division, Surgical Service, John Cochran (112JC), St. Louis, MO 63106

Office phone: 314-652-4100 ext 54463 Beeper: 314-491-2417
Home phone: 314-455-9482

P.S. I hope this e-mail will initiate an overall discussion regarding transparency by the agencies of the U.S. Government in regards to the EARLY (< 72 hours from diagnosis) administration with intent of synergism of COVID-19 Convalescent Plasma, COVID-19 monoclonal antibodies, Remdesivir and other future antivirals, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.

From: Public Affairs <Public_affairs@gilead.com>
Sent: Wednesday, February 16, 2022 7:54 AM
To: Andrus, Charles H. (STL) <Charles.Andrus@va.gov>
Subject: [EXTERNAL] Phase 1 remdesivir trial results

Dr. Andrus, You can find the published results of the Phase 1 remdesivir trial here:
https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.12840

Thank you for your inquiry,

Gilead Public Affairs

Discussion

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> On September 9, 1987, Dr. Harvey Cushing, then a resident in Surgery at The Johns Hopkins Hospital, operated on a patient with a ruptured appendix. The patient died ten days later of peritonitis. This experience must have increased his apprehension when, on Sunday, September 26, 1897, Cushing experienced abdominal pain and carefully recorded the development of his own episode of acute appendicitis (Fig. 14). At 9:00 am the following morning, he was seen in consultation by Drs. Halsted and Osler who did not advise operation. At 2:00 pm on the same day, he was taken to the operating room where Dr. Halstead removed his appendix. A somewhat complicated recovery followed (fig. 15).

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America's Fight Against Coronavirus, SARS-CoV-2, COVID-19
with mRNA vaccine prophylaxis (monoclonal *Active Immunization*)
alone *without implementation* FOR ALL infected with COVID-19 with
synergistic, early treatment (<96 hours from diagnosis) with exogenous immunoglobulins (*Passive Immunization*) and antivirals

OR

Euphemistical Obfuscation in Clinical Medicine, *Jesuitical* Lies by Omission and Paltering, Subliminal Bait-and-Switch, and Machiavellianism Resulting in 1,000,000+ Deaths and America's Defeat by the Non-sentient Coronavirus, SARS-CoV-2, COVID-19

Charles H. Andrus, M.D., F.A.C.S.
Former Professor (Tenured), Department of Surgery, Saint Louis University SOM
Former Professor and Vice-Chairman, Department of Surgery, Loyola University SOM and
Chief, Surgical Services, Edward Hines, Jr. VAH
Former Federal Whistleblower at the direction of the VA OIG and VHA Medical Inspector –
U.S. Office of Special Counsel, files MA-00-1107, DI-00-1147
U.S. Court of Appeals for the Federal Circuit, Case# 03-3162 (EEOC case 210A36145X)
NIAID Case #12276, U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)

150 Emerald Green Ct.
St. Louis, MO. 63141
314-265-1814

November 1, 2024

In a publicity website for the new memoir of Anthony Fauci, M.D., former Director of the National Institute of Allergy and Infectious Diseases (NIAID): *On Call – A Doctor's Journey in Public Service*[1], it opens with: "The memoir by the doctor who became a beacon of hope for millions through the COVID pandemic, and whose six-decade career in high-level public service put him in the room with seven presidents."[2] In his book at least 19 times, Dr. Fauci alluded to the compatibility of having had a Jesuit education and his devotion to public service.[1] In fact, during the first spring of COVID-19 U.S. epidemic, Dr. Fauci explicitly stated this in an interview with Dr. Howard Bauchner, M.D., then editor-in-chief of the *Journal of the America Medical Association* (JAMA)[3]:

> **Dr Bauchner:** Your equanimity, does it come from your parents? Does it come from your Jesuit education? It's extraordinary under the face of remarkable criticism, almost always unfair.
>
> **Dr Fauci:** I think it does come a lot from my parents. My father was very much of a tolerant person who would accept people for what they are and very rarely ever criticized anybody. I went to a Jesuit high school in Manhattan, and from there I went to a Jesuit college. I think it was just right for me because I had always been interested in public service and not being somebody that ever attacks anybody, that accepts them for who they are and what they are. So it was kind of the perfect atmosphere to me to be educated in, and I just carried it along with me.

I agree with Dr. Fauci that my years with Jesuit[4,5] education and my public service as a physician and surgeon of the Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (DVA) (Attachment I) Includes references 6-11, Andrus *Curriculum vitae* is reference 12 :

> St. Ignatius College Preparatory, SF, 1967-1971;
> University of San Francisco, BS in Chemistry, *summa cum laude*, 1971-1975;
> Saint Louis University SOM, Doctor of Medicine, 1975-1979;
> Residencies in Pediatrics, 1979-1981 and General Surgery, 1981-1986
> at the Affiliated Hospitals of St. Louis University SOM (SLUSOM);
> faculty, SLUSOM 1986-1996 and my public service as a Physician and Surgeon,
> Veterans Health Administration, U.S. Department of Veterans Affairs (1982-1996)
> faculty, Loyola University SOM, Chicago 1996-2001and my public service
> as a Physician, Surgeon, and the Chief of Surgical Services, Edward Hines Jr. VAH, Veterans Health Administration, U.S. Department of Veterans Affairs (1996-2002)
> faculty, SLUSOM (2006-2020) and my public service as a Physician and Surgeon,
> Veterans Health Administration, U.S. Department of Veterans Affairs (1982-1996, 2016-2022)

were compatible and paramount in my outlook as a physician and surgeon with all the altruistic mottos I have practiced under in Medicine and Surgery during my professional life[12]:

"Primum non Nocere" – First, do no harm Hippocrates [13-15]

Ad Majorem Dei Gloriam – To the Greater Glory of God St. Ignatius of Loyola [16-18]

…to care for him who shall have borne the battle, and his widow, and his orphan… Abraham Lincoln [19]

…Moreover, I promise to deal with each patient as I would wish to be dealt with were I in his position…
Fellowship American College of Surgeons Pledge [20]

…the secret in the care of the patient is in caring for the patient. Dr. Francis W. Peabody [21,22.]

"Men for Others" Father Pedro Arupe, S.J. [1,23-25]

By the very design of the University-VA affiliation of 1946, PL-79-293 [26,27] and VA Policy Memorandum #2 [28] and my personal involvement in the clinical and educational entities listed above, as an American Board of Surgery Certified General Surgeon, I[12] was employed professionally for 25 years[11- pages e262-e264] during my four decades as both an Academic and Federal Physician and Surgeon in the University-VA systems[29,30] which were established to be harmonious-in-intent and purposeful-in-focus regarding: First, and foremost, the care of our fellow man—and, in the case of the VA, the Veteran patient[7-14 as outlined in Attachment 1] as President Abraham Lincoln promised for all of us for all times:

> …to care for him who shall have borne the battle, and for his widow, and his orphan…[19]

On December 10, 1999, I was one of five physicians interviewed in the 10th floor "Secretary's Conference Room of VA Central Office (across Lafayette Square from *The White House*) by the VHA USH Commission for the position of the VA Under Secretary for Health (USH) 38 U.S. Code § 7301[31,32], U.S. Department of Veterans Affairs (Andrus[7-13], Bowen[10,33], Garthwaite[10,34,35], Petzel[10,36-41], Roswell[10,42-43]). As Dr. Bowen's name and mine were not advanced to *The White House* for subsequent vetting and ultimate submission and approval by the Senate to the position of VHA USH, my daily role for over 25 years of officially-documented public service[11- pages e262-e264] in the VA was principally that of a General Surgeon, Clinician, funded Researcher for a 4-year period of time, and as an advocate for my patients within the U.S. Department of Veterans Affairs.[12] While Dr. Fauci may have been "in the room of seven presidents"[2], I was probably considered more of an annoyance (burr-in-the-saddle) to only the five most-recent presidencies in my advocacy for appropriate patient care <u>for all</u> throughout my 32 years as an Attending Physician and General Surgeon in the Jesuit[4,5] medical school educational system and ~25 years within the U.S. Department of Veterans Affairs.

Ironically, other participants throughout history who attended or taught within Jesuit[4,5] education in the past besides Dr. Fauci[1] and myself[12] are: Sir Arthur Ignatius Conan Doyle[44], René Descarte[45], Pope Francis[46], Fidel Castro[47], former President Bill Clinton (1993-2001)[48], Associate Supreme Court Justice Clarence Thomas[49-50], Associate Supreme Court Justice Neil Gorsuch[51-53], Associate Supreme Court Justice Brett Kavanaugh[51-53], and former President Donald J. Trump (2017-2021)[54-56]—to name just a few. While Justice Thomas[49] and I[12] were inducted into the Jesuit[4,5] Honor Society--AΣN[57]–during our undergraduate collegiate years, recently Dr. Fauci became an honorary AΣN member through Georgetown University in the acknowledgement of his pivotal role in our nation's fight during the COVID-19 epidemic.[58,59] In the religious formation, instruction, and development of a Jesuit[4,5] scholastic and/or newly ordained priests and brothers (trainees of the Society of Jesus[4,5] of the Catholic Church—*The Jesuits*[4,5]), one of the courses of study is that of Apologetics[60]—the art of the debate in the defense of the Faith. While the term *Jesuitical*[61,62] primarily means being a member of the Society of Jesus[4,5], the second alternate meaning has a pejorative connotation of being *slickly equivocal*. Hopefully, not exploiting the second definition of *Jesuitical*[61,62], I will employ in this paper the apologetical technique of *reductio ad absurdum* [1,11,12,63-65] --Attachment II—<u>*reduce the argument to the absurd*</u>--to point out how we, all too often, as a society and especially today in the Practice of Medicine, have fallen into the trap of believing that which individually suits us for self-promotion and advancement (much too often to the detriment of others).

Such a mindset is a prevalent, all-too-common, subliminal form of the application of Machiavellianism[66-68] in our present-day American society: *The end justifies the means*.[69-70] At all levels of American life today (e.g.: personal interactions, business, academia, politics, and, most especially Medicine), *the end justifies the means*[69-70], has become all-too-pervasive, subliminally surreptitious, and blatantly a bait-and-switch[71] fostered by **lies of commission, lies of omission, and paltering**.[72-76]

Such is in contrast to ***Veritas Vincit Omnia*[77-78] -- *Truth Conquers All.*** While a half-of-a-millennium overdue, in December 1999, St. Pope John Paul II apologized to the Bohemian people (today the Czech Republic) for the execution of Jan Hus who is credited in publicizing the phrase *Veritas Vincit Omnia* in 1413. Today, does Jan Hus' admonition: *Veritas Vincit* Omnia even have any relevance in American society?

Prior to this article's in-depth analysis of U.S. Medicine's emphasis during the COVID-19 pandemic on vaccination/**PROPHYLAXIS** for COVID-19 (Active Immunization) and failure to utilize in an organized fashion early **TREATMENT** (within 72-96 hours after diagnosis) with immunoglobulins (Passive Immunization) and antivirals, what immediately follows are a few examples of foundational and historical disregard of *the facts*, obfuscation of the truth, and **lies of commission or omission and/or paltering** —some are innocuous while others have had the potential to lead us to a societal retrogressional mindset:

Example 1, **Paltering** *(The Methodology of the Riddle):* While on a car-rally-date on a Saturday night during my college years, I was posed with the inconsequential riddle at one of the rally-route checkpoints which went something like this:

> If a rooster is perched on the peak of a barn roof with the pitched sides of the roof facing west to east, the western portion of roof being angled at ~10 degrees while the eastern portion is at ~5 degrees, and the wind is blowing from west to east at 15 knots, when the chicken lays the egg, which side of the barn roof will it roll down?—After a moment of consideration, the correct answer was that roosters don't lay eggs.

While the rooster perched on the barn roof, the dimensions of the barn, the direction and speed of the wind, and that chickens lay eggs are individually truthful, this is a harmless, somewhat humorous example of ***Paltering***[75] in which:

> **Paltering** is active use of truthful statements to convey a misleading impression. …

All too often today in our analysis in applying foundational / fundamental information, we become distracted by the extraneous rhetoric and subliminal lies of commission or omission and fall victims to our yearnings to rush to a judgment for a definitive conclusion disregarding foundational teachings and doctrine.

Example 2, **Errors of Omission**: Throughout the Biden administration, one of the major focused environmental projects has been the removal of all y66 pipes from all potable water

systems throughout the United States.[79-88] While water systems contaminated from lead pipes, lead solder, galvanized pipes contaminated with lead *ortho*-phosphate, etc. are probably the major ongoing cause of lead exposure throughout the United States, the EPA still proports to all rehabilitation-contractors that[89]:

> **WHERE DOES THE LEAD COME FROM?**
>
> **Dust is the main problem.**
>
> The most common way to get lead in the body is from dust. Lead dust comes from deteriorating lead-based paint and lead-contaminated soil that gets tracked into your home. This dust may accumulate to unsafe levels. Then, normal hand to-mouth activities, like playing and eating (especially in young children), move that dust from surfaces like floors and window sills into the body.

Since the 1990s, though, most water systems throughout the United States have employed *ortho*-phosphate additives precipitating lead salts in lead pipes and also in downstream galvanized iron (and cast iron) pipes thus decreasing the solubilized concentrations of the oxides and hydroxides of lead ions.[90-91] When Flint, Michigan switched from Detroit water to its own sources, addition of *ortho*-phosphates were mistakenly overlooked and subsequently the tap water downstream from lead pipes and in the older homes of Flint which had cast iron pipes downstream from the lead pipes feeding their homes and/or galvanized pipes within the homes turned red, smelled, and tested positive for high levels of lead (Pb).[93-96] As long as there is galvanized/iron piping in individual housing, businesses, playground water-fountains, etc. that were previously downstream from lead pipes whose water supplies were treated with *ortho*-phosphates, increased levels of lead will continue to be detectable in the populous of our country due to the slow solubilization of precipitated lead salts over time from contaminated corroded pipes previously downstream from the lead pipes as was noted in a JAMA Pediatrics article of March 18, 2024: "Estimated Childhood Lead Exposure from Drinking Water in Chicago." While removal of all the lead pipes in this country has been estimated to take at least a decade into the future to accomplish, (1) what of the downstream iron pipes that are contaminated by precipitated lead phosphates[90,91,93- 96] and (2) what about the other associated ongoing human morbidity?[98] Should chelation therapy be advocated for those testing positive for elevated serum lead levels as our water supplies are being extirpated of lead contamination?[99,100]

While removing all the lead pipes in drinking from throughout the United States is a medically and ethically mandated project[101-102] long overdue, the omission of the consideration of the downstream internally-rust-corroded iron pipes contaminated with lead *ortho*-phosphate precipitates throughout the nation over the last 2-3 decades is an ongoing environmental and epidemiological silently ubiquitous catastrophe. The most recent review article entitled Lead Poisoning in the *New England Journal of* Medicine of October 31, 2024 provides an extensive history but fails to mention downstream galvanized/iron plumbing nor orthophosphophosphates.[103] Whether calculated or unintended, the disregard / **omission** of the knowledge of the solubility of lead in drinking water—no matter how small—is affected by phosphate additives in the water and most consistent with what occurred in Flint, Michigan[104]:

> Hydroxypyromorphite (HPM) is a low-solubility Pb phosphate mineral that has the potential to limit solubility and bioavailability of Pb in soils and water. Because of reported uncertainty regarding the solubility product of this important mineral, we re-evaluated the solubility of Pb and activity of the free

> Pb2+ ion in aqueous suspensions of microcrystalline HPM equilibrated up to 30 days over a wide range of added soluble phosphate. A small addition of phosphate (0.1 mM) reduced Pb solubility as measured by ICP-OES, but greater phosphate additions (up to 50 mM) had no further effect in lowering HPM solubility. However, free Pb^{2+} ion activity measured by ion-selective electrode progressively decreased from about $10^{-6.5}$ with no added phosphate to 10^{-9} as soluble phosphate was increased. The effect of soluble phosphate in lowering Pb^{2+} activity is attributed to inhibited dissolution of HPM as well as increased $^{Pb2+}$-phosphate ion pair formation in solution at higher solution concentrations of phosphate. Measurement of the ion activity products (IAP) of the solutions at equilibrium with HPM gave highly variable IAP values that were sensitive to pH and were generally not consistent with the reported solubility product of this mineral. The high variability of the IAPs for solutions with variable pH and phosphate concentrations indicates that dissolution precipitation reactions of HPM are not described by a constant solubility product at equilibrium, possibly because of the incongruent dissolution behavior of this mineral at near-neutral pH.

By the simple **Omission** of disregarding *the finite solubility of an inorganic compound in solution*, United States society has condemned *ad infinitum* anyone drinking water from contaminated galvanized / iron pipes that are or were downstream of lead pipes treated with *ortho*phosphates for any period of time to the potential of continued chronic lead exposure.

Example 3, **Lies of Commission and Omission, Paltering, and Political Meanness and Immorality**: In the Winter of 2023-2024, anticipated Republican-presidential-nominee Trump persuaded the Republicans of Congress to disavow a bipartisan bill of the Senate for immigration reform so he could make immigration reform the keystone issue of his campaign for President of the United States in 2024.[105-109] Migrants on the USA/Mexican border were demonized in the media by the former President[110-114]; migrants were transported across state lines to northern cities [115-119] at the approval of legislatures and governors of some of southern states in what, I would allege, were violations of the Lindbergh law of 1932, PL-72-189, 18 U.S.C. 1201 [120]; and potentially-passive lethal impediments were deployed in defiance of a U.S. Supreme Court ruling.[121-124] Does the Governor of a State with no border contiguous with the country of Mexico[125] have the authority to send the National Guard when according Article I, Section 8, Clause 11 of the U.S. Constitution only Congress has the authority to declare war?[126-128] On the other side of the argument, could the President of the United States federalize those same National Guard troops to perform humanitarian efforts with regards to all those not-of-this-country that are crossing the border?[129-132] Ironically, the National Guard sent to the U.S.-Mexico border could be federalized by the President to do good for these desperate people rather than create impediments to their very existence.

It is estimated by the U.S. Border Patrol that from FY 1998 to 2022, about 9,520 migrant deaths[133-136] were reported within U.S. borders of the continental United States of America in their attempts to cross the Mexican/USA border. So much for:

> 1) We hold these truths self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty and the pursuit of Happiness.—That to secure these rights, Governments are instituted among Men, deriving their just powers from the consent of the governed,--That whenever any Form of Government becomes destructive of these ends, it is the Right of the People to alter or to abolish it, and to institute new Government, laying its foundation on

such principles and organizing its powers in such form, as to them shall seem most likely to effect their Safety and Happiness. from the Declaration of Independence[137]

2) …"Give me your tired, your poor,
Your huddled masses yearning to breathe free,
The wretched refuse of your teeming shore.
Send these, the homeless, tempest-tost to me,
I lift my lamp beside the golden door!" from Emma Lazarus's sonnet about the Statue of Liberty[138]

To modify the stalemate, President Biden worked throughout 2023 to facilitate a bipartisan effort to address the problem[139,140] but finally unilaterally announced on June 4, 2024, new actions to secure the border.[141] In short, though:

The underlying moral barbarism still remains--Disregard for Individual Human worth of which we should all be ashamed![142-145]

Example 4, **Paltering in the Analytical Evaluation and Analysis, Resultant Public Health Policy Misdirection, and Untreated Deaths for over a quarter of a century**:

Since 1998, the monoclonal antibody palivizumab (Synagis)[146,147] was approved as a prescription drug in the prophylaxis of Respiratory Syncytial Virus (RSV)[148-150] by the FDA in high risk neonates/infants only. Prior to the COVID-19 American epidemic in 2018, Dr. Fauci as the senior author of[151]:

> Marston HD, Paules C, Fauci AS: Monoclonal antibodies for emerging infectious diseases – Borrowing from history. N Engl J Med 2018 Apr 19; 378 (16): 1469 – 1472. https://www.nejm.org/doi/10.1056/NEJMp1802256?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed , https://www.nejm.org/do/10.1056/NEJMdo002465/full/

was interviewed by Dr. Morrissey of *The New England Journal of Medicine* and stated[152]: https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area=:

> Well, for example, a classic monoclonal antibody for prophylaxis against Respiratory Syncytial Virus has been developed with considerable success. …

While the monoclonal antibody palivizumab against RSV is one of present-day immunological science's greatest success stories per the interview of Dr. Fauci and one of the best examples of Passive Immunization[153-159], (and now nirsevimab[160-165] (Beyfortus)), it has been *de facto* rationed in clinical medicine since 1998 directed solely by the FDA as **prophylaxis only** in high-risk infants.[159-172] The adult medical literature has completely ignored palivizumab as an early (<96 hours from diagnosis) passive immunologic treatment of RSV for all. Since 1998, the CDC has reported an annual mortality of 300 in children and in adults over age 65 from 6000-10,000 individuals per year which calculates to 150,000 to 250,000 untreated deaths in adults over age 65 years over the last quarter century.[173-175] While treatment in infants[176-178] has been studied with no difference in length of hospitalization used as the only endpoint[179-187], there have

been no studies regarding treatment (not prophylaxis) at any age group with the endpoint being death (which is 200-330 times greater annually in adults than children). This **paltering application and FDA-directed practice of medicine regulating** palivizumab by *de facto* rationing with FDA approval of **prophylaxis only in infants only**[164-171] —and not treatment to prevent death--is akin to the unethical withholding of penicillin for treatment in the Tuskegee Syphilis Project[188,189] of the mid-twentieth century--but at a national level. For the last quarter of a century, a magnified total death toll in adult RSV disease has been documented by the CDC to be 250-400 times when compared that observed resultant in the participants in Tuskegee Syphilis Project (due fortuitously to the limited patient population (~600 patient subjects—399 with syphilis and 201 controls without syphilis) in the Tuskegee Syphilis Project.

As an editor since 1983, Dr. Fauci's name[1(pp.237-238)] is recognizable "from the frequently updated medical textbook *Harrison's Principles of Internal Medicine"*[190] to the large number of physicians who were exposed to this major textbook: "… while they were in medical school and during their residency training." To the present, Dr. Fauci has been an editor of eleven editions (11th-21st editions) of which he was the overall editor-in-chief of two: the 14th and 17th editions.[190, p ii] Without ever explaining the logic and principles of immunology or clinical medical practice since 1998 of restricting palivizumab to prophylaxis in high risk infants only, palivizumab is mentioned five times in the greater than 3855 pages of the 21st edition of *Harrison's Principles of Internal Medicine*[190]:

1. Both RSV and parainfluenza viruses, particularly type 3, can cause severe or even fatal pneumonia in HSC transplant recipients. Infections with both these agents sometimes occur as disastrous nosocomial epidemics. Therapy with palivizumab or ribavirin for RSV infection remains controversial. (page 1140)

2. ***Palivizumab*** Palivizumab, a humanized monoclonal antibody to RSV F protein, is approved for prevention of lower respiratory tract disease due to RSV in pediatric patients at high risk of RSV disease, including premature infants and children with bronchopulmonary dysplasia. (page 1464)

3. **PASSIVE PROTECTION WITH IMMUNOTHERAPY**
Palivizumab, a humanized mouse monoclonal antibody to the F protein of RSV, is licensed for prevention of RSV hospitalization in high-risk infants, in half or more of whom it is effective. (page 1513)

4. Palivizumab, 1140, 1464, 1513. (page I-164)

The foundational essence of the FDA's regulatory functions began in 1906 with the enactment of the Pure Food and Drugs Act, PL-59-384.[191-193] The history [194-205] of its mandate to regulate and protect the American public (never to dictate medical practice) has progressed, evolved, and matured over the years.[206,207] Unfortunately, although the RSV story over the last twenty-five years is mired in confusion regarding treatment versus prophylaxis and selection bias between pediatric and adult internal medicine research, application in clinical Medicine today is best typified by the ancient parable of India of the Blind Men and the Elephant.[208] What has resulted today is a hodgepodge of processes and policies that exclude or ignore appropriate application of passive immunization and antivirals *as treatment* during the viremic phase of a viral infection (<72-96 hours). In essence, the FDA regulations have been used to develop restrictive policies *de facto* proscribing immunoglobulin treatment uses in infected individuals with the resultant consequence of the FDA *de facto* prescribing daily Clinical Medical Practice devoid of early immunotherapy at all ages which was never the intent nor within the scope of the legal mandate of the U.S. Food and Drug Administration.

A prospective study using palivizumab as a *Passive Immunization* **treatment** was performed in RSV infected infants[177] and no difference was demonstratable in which the only chosen primary endpoint of hospital length-of-stay which has too many associated variations fails to study that which should be the primary endpoint of death. As the incidence of annual mortality from RSV in infants (~300 per year) and in adults is 6,000 – 10,000 per year[173-175, 209], death as the primary endpoint in a randomized controlled trial (RCT) would not be finitely feasible and would be considered unethical. Even still, no comparable RTC utilizing length-of-stay as the primary endpoint in adults has been reported. Even though the adult mortality is estimated to be 20 times higher than that of infants, a prospective RCT with palivizumab and/or nirsevimab as *Passive Immunization* treatments early (not prophylaxis) in the course of the disease (<72-96 hours) still would not be feasible with death as the endpoint as the annual mortality incidence is small in adults and any RCT would not be finitely feasible and would be considered unethical. With a previous 25-year national experience, though, an age-matched controlled trial (AMCT) with palivizumab or nirsevimab as ***Passive Immunization*** **treatments** versus historic control non-immunologic treatments would be feasible and ethical.

Until recently (2023 going forward), the statement: "There are currently no targeted prophylactic, therapeutic, or vaccine options for RSV in older adults, and treatment is limited to offering supportive care for adults with the illness"[209] was true due in a large part to the paucity in research in therapeutically addressing RSV in adults[209]:

> RSV bronchiolitis is the leading cause of infant hospitalization due to viral respiratory illness, characterized by respiratory distress that can result in death. There is no specific treatment for RSV, only supportive care measures like oxygen and fluids. Currently, there is no vaccine to help prevent RSV in the U.S., leaving most infants without protection. The only available preventive agent is recommended for use among the highest-risk infants in limited settings as a monthly injection with five doses administered during the RSV season.
>
> Among adults 65 years and older, RSV infections account for approximately 60,000–160,000 hospitalizations and 6,000–10,000 deaths each year in the U.S. alone.[11,12,13,14,15,16,17,18] There are currently no targeted prophylactic, therapeutic, or vaccine options for RSV in older adults, and treatment is limited to offering supportive care for adults with the illness.

With the development of the RSV vaccines[209-214] (Active Immunization), prophylactic protocols are now being aggressively promoted and marketed[215-218] for adults 65-74 years of age and >75 years and pregnant mothers between 32 and 38 weeks gestation [219-223] without any overall/universal immunological principle/protocol explanations regarding treatment of infected individuals. While the vaccine in the mother stimulates endogenous immunoglobulins production by *Active Immunization* in the mother, the fetus receives these immunoglobulins via the placenta of the mother as exogenous immunoglobulins by *Passive Immunization* with the finite life-span in the child of 2 - 6 months ($t_{1/2}$= 36-38 days).[159,162] Administered exogenous RSV monoclonal antibodies reportedly have half-lives of: $t_{1/2}$= 21-88 days for palivizumab[159] and $t_{1/2}$ of 68.7 $\pm$ 10.9 days for nirsevimab[224] (and, for nirsevimab, a half-life range of 80 – 120 days[167,225]).

Like with other members of the *Paramyxoviridae* virus family (mumps, measles viruses, etc.)[226,227], a more prudent long-term, epidemiologically-sound mandated process would be to

vaccinate every child (the vectors for the family and society) at ~6 months to 1 year of age with a subsequent booster at ~6 years to promote the long-term minimization of the annual seasonal epidemics of bronchiolitis, etc. When any individual regardless of age requires hospitalization due to RSV infection, then *Passive Immunization* (e.g.: palivizumab[146-172,177,190], nirsevimab [160-165,167,224,225], etc.) and antivirals treatments (e.g.: ribavirin (virazole) and other chemotherapeutic agents in the future)[228-230], should be administered regardless of previous vaccination status as these treatment maneuvers, especially synergistically, may be life-saving.

The **Paltering** story of the prophylaxis and lack-of-treatment of Respiratory Syncytial Virus (RSV) infections in children and adults is riddled with ignorance, incomplete analyses, and aggressive marketing by the pharmaceutical companies producing vaccines and continuing restrictions of the monoclonal antibody **Palivizumab** by the FDA of a quarter of a century to only high risk infants with the exclusion of non-high-risk infants, children, and adults. (One of the overriding subliminal prohibitive restrictions in the treatment (not prophylaxis) of RSV with palivizumab can be summed up in the statement: ***"However, palivizumab is only available for high-risk children in developed countries due to prohibitive costs."***[230])

Ironically, in **the phase I study of the extended half-life MEDI8897** (NCT02114268) [231, 232], "a fully human anti-RSV prefusion F monoclonal antibody with increased potency and an extended half-life" was carried out not in children or infants but in healthy adults ages 18 to 49 years with the following results[231]:

> Except for 1 subject who had a 4-fold increase in neutralizing antibody titer, possibly due to an RSV infection or exposure, subjects in the placebo group had stable titers for the duration of the study (mean titer range, 8.2 to 8.6 $\log_2$). Among those receiving MEDI8897, RSV neutralizing antibody titers increased in a dose-dependent manner (Fig. 3). The highest titers were detected 8h postinfusion in those receiving an i.v. dose and on day 6 in those receiving an i.m. dose. At 8 h postinfusion, the geometric mean fold rise in titers was 0.96, 27.4, 33.8, and 96.0 among subjects receiving placebo or MEDI8897 at 300 mg i.v.., 1,000 mg i.v., and 3,000 mg i.v., respectively. This geometric mean fold rise in titers on day 6 was 1.1, 13.6, and 12.5 for placebo, MEDI8897 at 10 mg i.m., and MEDI8897 at 300 mg i.m., respectively. On day 31, neutralizing antibody titers had increased ≥4-fold relative to baseline levels in 100% of subjects receiving an i.v. dose of MEDI8897 and 83% and 91% of subjects receiving 100 mg i.m. and 300 mg i.m.MEDI8897, respectively. This ≥4-fold increase in neutralizing antibody titers from baseline persisted until day 181 in 60%, 80%, 83%, 50%, and 55% of subjects receiving 300 mg i.v., 1,000 mg i.v., 3,000 mg i.v., 100 i.m., and 300 mg i.m. MEDI8897, respectively. Neutralizing antibody titers were lower in the 300-mg i.m. group than in the 300-mg i.v. group at 8 h following administration but were comparable at day 6 through the end of the study. In general, administration of MEDI8897 resulted in increased levels of neutralizing antibodies that were maintained above background levels for up to 1 year.

MEDI8897 is the "Other product name(s)" for the FDA approved established/proper name *Nirsevimab* and the "(Proposed) proprietary name" of *Beyfortus*.[233] "In July 2023, the Food and Drug Administration approved nirsevimab[160-164,167-170,172,178,231-237], "a long-acting monoclonal antibody, for passive immunization to prevent RSV-associated lower respiratory tract infection among infant and young children."

Regardless of financial constraints resulting in immunoglobulin and antiviral rationing and selective capital opportunities for pharmaceutical company profits[228,230], hopefully, in the future an organized, **truthful**, clinical algorithm will be established in the *Passive Immunization* treatment, as well as, prophylaxis—not just infants—**BUT for all ages.** Who will organize such

a process (e.g.: NIH, FDA, PHS, CDC, Academic Medicine, *Harrison's Principles of Internal Medicine*[190],etc.)? And, if an organized set of protocol(s) are developed, how will such protocols utilizing appropriate, comprehensive, all-inclusive *Active* and *Passive Immunization* and antiviral therapies enter into the general medical literature so as to encourage daily clinical applications to encompass and be appropriately implemented for all stages of life **in the treatment (and prophylaxis)** of RSV infection in: the fetus, the neonate, all family members regardless of age, and the >60 year-old population?

CONCLUSION:

America's Fight Against Coronavirus, SARS-CoV-2, COVID-19
with mRNA vaccine prophylaxis (monoclonal *Active Immunization*) alone *without implementation* FOR ALL infected with COVID-19 with
synergistic, early treatment (<96 hours from diagnosis) with exogenous immunoglobulins (*Passive Immunization*) and antivirals
OR
Euphemistical Obfuscation in Clinical Medicine, *Jesuitical* Lies by Omission and Paltering, Subliminal Bait-and-Switch, and Machiavellianism Resulting in 1,000,000+ Deaths and America's Defeat by the Non-sentient Coronavirus, SARS-CoV-2, COVID-19

was an explanation of the previous definition of the terminology of ***PALTERING*** with some unrelated but pertinent examples of the pervasive methodology of ***PALTERING.*** In our American society today, ***paltering*** permeates our daily societal interactions pervasively throughout all walks of life especially in medical explanations to the American public. Specifically, this in-depth dissertation on ***Paltering*** is **Attachment I** to the paper:

Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals (Not Prophylaxis/ Active Immunization) in Persons Infected with COVID-19

regarding the American COVID-19 Epidemic in which U.S. Medicine and the American public were inundated with a potpourri of disorganized facts, theories, and political maturations. In our response to COVID-19, U.S. Medicine organizationally:

(1) failed to outline for the American public the pathophysiology of a SARS-CoV-2 infection,

(2) failed to make the distinction between **Treatment** of an infected individual (with i.e.: Immunotherapy—*Passive Immunization* and Antivirals) and **Prophylaxis** (with i.e.: vaccines-*Active Immunization)*, and, in so doing,

(3) U.S. Medicine facilitated / tolerated a **disregard and dismissal for the early treatment** (not prophylaxis) within 72-96 hours of diagnosis of individuals infected with coronavirus, SARS-CoV-2, (COVID-19) with the appropriate application of exogenous immunoglobulins and antivirals in an organized, non-rationing, financially-equitable fashion, etc.

The rest of these **Attachments (II – VII)** provide other documentation that address, analyze, and discuss other facets regarding the failure to develop an appropriate, organized early treatment (<72 – 96 hours from diagnosis) of every individual infected with coronavirus, SARS-CoV-2, regardless of individual's vaccination status. On April 1st, 2020, (seemingly *apropos* as April 1st is April Fools Day) Nora O'Donnell on the nightly CBS News posed the following inquisitorial statement after which Dr. Fauci responded with a self-apparent truism which has epitomized the last five years of America's confrontation with the COVID-19 global pandemic[238]:

> Norah O'Donnell: With all due respect it does seem like so much of this we're making it up as we go along.
>
> Dr. Anthony Fauci: Well, you know you make it up as you go along, Norah, because that's what you know—that's where the war is all about. I don't like to necessarily make that analogy to a war, but if you talk to the generals with experience, you have a plan. But when the bullets start flying, everything becomes a fog, and you have to play it by ear. We do have a good plan. We need to be humble that we don't know all the answers, and we don't know how exactly this is going to turn out.
>
> Norah O'Donnell: Dr. Fauci, thank you so very much for your time and expertise.
>
> Dr. Anthony Fauci: It's always good to be with you, Norah. Thank you.

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>
> > **(3) Level 3.** The staff practitioner is immediately available in the facility – campus for direct resident supervision according to local policy as approved by the Network Academic Affiliations Officer. The service chief is responsible for periodically reviewing cases done under Level 3 supervision to ensure that such supervision is appropriate.
>
> Using the Wayback Machine another version of the Level 3 Supervision (now Level D) is identified: In VHA Handbook of July 27, 2005 signed by Jonathan B. Perlin, M.D. https://web.archive.org/web/20051107072236/http:/www.va.gov:80/OAA/1400_1hk_July27_05.doc (Recission of the previous version of May 3, 2004 which cannot be found):
>
> > 4. **Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and immediately available for resident supervision or consultation as needed.

Using the only other "hit" on the Wayback Machine of December 21, 2016, http://web.archive.org/web/20161221045318/http://www.va.gov/oaa/1400_1hk_Oct2001.doc VHA 1400.1 has been removed completely and in its place is the website of the U.S. Department of Veterans Affairs which states: "Page Not Found." ***De facto*, the U.S. DVA, VHA**

misdirected official government documentation which is tantamount to destruction of evidence used in the trial of Andrus v VA, U.S. Court of Appeals for the Federal Circuit, docket # 03-3162.

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38. Petzel RA: Resident Supervision. VHA Handbook 1400.01, Veterans Health Administration, U.S. Department of Veterans Affairs, 19 Dec 2012 https://www.va.gov/OPTOMETRY__/docs/VHA_Handbook_1400-01_Resident_Supervision_12-19-2012.pdf

> **5. RECISSIONS.** VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005 is rescinded……. (page 1). [***Please note that when one searches for VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005, one is redirected to VHA Handbook 1400.01. Using the Wayback Machine and the previous URL for VHA 1400: http://web.archive.org/web/20161221045318/https://www.va.gov/oaa/1400_1hk_Oct2001.doc , one can find the 2001 version in the 2004 of the Internet Archive captures. There are no other captures of this URL in the Wayback Machine except December 21, 2016 which brings up the VA Website which states: "Page Not Found."***
>
> **4. Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and able to provide direct supervision or consultation without delay as needed. (page 9)

39. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063, Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. The original version of VHA Directive 1063 of December 24, 2013 which claimed physician assistants could be independent practitioners -- which I would allege is a violation of every State Medical Boards' credentialling policies/laws regarding Physician Assistants. In the 2013 version, the justification of the violation of all State Medical Boards was in 2.c:

> Under the Supremacy Clause of the U.S. Constitution, States are prohibited from regulating or controlling the activities of the Federal Government without written Congressional consent; where Federal and State laws conflict, Federal law governs official actions of Federal employees. Examples of the types of activities that the Federal Government may establish are qualifications for employment and scopes of practice. Therefore, the establishment of scopes of practice for VA PAs defined by this Directive is without regard to State Practice Acts.
> https://web.archive.org/web/20140814150238/https:/www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958

40. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063 (1), Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. Captured on July 22, 2023, by the *Internet Archive.* https://web.archive.org/web/20230722070741/https://www.va.gov/VHAPUBLICATIONS/ViewPublication.asp?pub_ID=2958 In **2. SUMMARY OF CHANGES** of the **Transmittal Sheet** which is still labelled **December 24, 2013** but in red has stamped: **AMENDED May 17, 2022** is: (1) Paragraphs 2.c. and 2.e. removes references to the Supremacy Clause reference and physician liability.—which means that the independent practice of a VHA Physician Assistant was rescinded returning all Physicians Assistants to the State Medical Board statutes outlining mandatory Physician scope of practice affiliations and legally mandated Physician oversight. The signatory official on this document is Robert A. Petzel, M.D., Under Secretary for Health who had been terminated over the Phoenix VAMC scandal 8 years prior to this as noted above in references 36 and 37.

41. Petzel RA: Utilization of Physician Assistants (PA) VHA Directive 1063(2), December 24, 2013 AMENDED June 24, 2024. When one uses a search engine like GOOGLE or enters the official URL of this document site: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 , one is electronically shifted to a .pdf file, e.g.: file:///Users/andrusmd1/Downloads/1063(2)_D_2013-12-24%20(6).pdf. The https://... URL version was captured by the *Internet Archive* on July 18, 2024. The signatory official on this document is still Robert A. Petzel, M.D., Under Secretary for Health, who had been terminated over the Phoenix VAMC scandal 10 years prior to this as noted above in references 36 and 37. https://web.archive.org/web/20240718212213/https://www.va.gov/VHApublications/ViewPublication.asp?pub_ID=2958

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After OIG Inspector Griffin's testimony on May 8, 2003, ABC *Primetime* investigated for an entire year and on April 8, 2004, aired Fighting for Care narrated by Diane Sawyer. 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212) This episode was removed from the ABC Archives possibly because ABC to hidden cameras into the Cleveland and Temple, TX VAMCs. 2004 George Polk Award for "**Television Reporting: Diane Sawyer** and **Robbie Gordon**, ***ABC News PrimeTime Live***, for **"Fighting for Care,"** which documented patient abuse and deplorable conditions in VA hospitals." (for investigative reporting excellence) https://liu.edu/polk-awards/past-winners#2004. When Tammy Shehari, the Associate Producer for the episode, spoke with me by phone in 3/2004, she asked me to estimate how many additional veterans had died due to unsupervised operations performed by Surgery Residents– I declined to guess because to do so would be wrong and a disservice to the Veteran patients and the men and women of Department of Veterans Affairs that do their duty faithfully for Veteran patients. (The interview ended shortly after my refusing to guess, and this was the only time ABC News spoke with me.)

Please note the reference above -- VHA USH, Robert Roswell, M.D. resigned three days prior to the airing of *Fighting for Care*. *Fighting for Care* contained within unauthorized hidden cameras in the Cleveland VAMC and the Temple TX VAMC. The VA spin was: …Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. …. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

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>
> Prior to the use of antibiotics, antibodies were the only specific agents for the treatment of certain infections. Although this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1). Since several excellent reviews are available, this article will emphasize new developments (30, 31, 101, 164, 165).
>
> Antibodies can be administered as human or animal plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or convalescing donors, and as monoclonal antibodies (Mab) (30, 164,178). The therapeutic use of Mab is increasing dramatically, but only one (palivizumab for respiratory syncytial virus [RSV]) has been licensed for prophylaxis of an infectious disease.

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Footnote at bottom of every page of this Annotated Bibliographic Timeline:

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

This submission is NOT for financial gain but for educational purposes only for ALL the American people

Reductio ad Absurdum:[1]
The COVID-19 Tale of Two Presidents, the Ramifications of Fifty Years of American Scandal, Therapeutic Nihilism, and Medical Stupidity:

Euphemisms[2]**:** Experimental / Investigational / EUA[3],
Expanded Access[4] / Compassionate Care
FDA Authorization vs FDA Approval[5,6],
Treatment vs Prophylaxis[7],
Active Immunization[8-9] vs Passive Immunization[10,11], etc.,

FDA Archiving reliance on non-governmental sites[12,13]

FDA archived web material is maintained within the Pagefreezer platform.

and loss of information by ***electronic overwriting*** and ***destruction*** of URLs[14-16],

FDA and NIH blatant, total disregard of the Right to Try Act (PL-115-176)[17] by never declaring a completed Phase 1(Safety) [vs Phase 2/3 Efficacy] Clinical Trial[18-24] and thus dismissing and *de facto* legally violating PL-115-176[17]

Statistical Misdirection[25-28]**,**

Predatory Marketing[29]**,** and

> 1.1 million Americans dead[30] associated with **withholding early** (**within 72-120 hours** of diagnosis) synergistic treatment with **Exogenous Immunoglobulins (Passive Immunization)**[10,11] and **Antivirals**[31]

Contingent on: Ignorance[32], Sins of Ommission[33-34], Conflicts-of-Interest[35-36], Greed[37]

"Reform must come from within, not from without. You cannot legislate for Virtue" [38]
James Cardinal Gibbons, "Prince of Democracy"[39]

Charles H. Andrus, M.D., F.A.C.S.[40]
Former Physician and Surgeon, Veterans Health Administration
U.S. Department of Veterans Affairs
U.S. National Institute for Allergy and Infectious Diseases (NIAID) Case# 12276
150 Emerald Green Court, St. Louis, MO 63141
Home phone: 314-455-9482, Cell: 314-265-1814
April 26, 2023 **(Draft article for Educational Purposes only)**

Introduction:

A Century ago, the United States of America addressed monumental sociopolitical medical evils like:

> The Spanish Flu Epidemic of 1918 with *Passive Immunization (Convalescent Plasma)*[41-43];
>
> Substandard Medical Schools with the Flexner Report (1914)[44];
>
> Generally deplorable medical care in hospitals by oversight of the American College of Surgeons (1913)[45];
>
> Tainted foods and medical quackery with the establishment and empowerment of the U.S. Food & Drug Administration (FDA)[46].

In this new millennium, some of our foundational intents and tenents have been subjected to the misapplication of the Golden Rule[47]: *"Do unto others as you would have them do unto you"* that have evaded and, in some instances, besmirched and discarded ethical principles we uniformly profess during the World's confrontation with coronavirus, SARS-CoV-2, COVID-19 Pandemic![48]

Originating during the Winter of 2019 in Wuhan, China[49], a global epidemic (pandemic) arose due to the coronavirus, SARS-CoV-2 which overwhelmed the medical response around the world. In a television summary interview of the previous eighteen months of the COVID-19 pandemic airing on the Columbia Broadcasting System (CBS)'s *Face the Nation*[50] on November 28, 2021, the interviewer, Margaret Brennan[51], queried and Dr. Anthony Fauci, M.D.[52], Director of the National Institute of Allergy, responded:

> MARGARET BRENNAN: But just to button that up. Why aren't we having a national conversation about what went wrong? I mean, apart from this room right now, why isn't there a 9/11 type commission?
>
> DR. FAUCI: Yeah, I think what's going to happen is that you are going to see that for sure, MARGARET. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through with already 760,000 Americans dying and 40 plus million at least being infected, close to six million people globally dying. **And we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out. So people should not think that that's not going to happen. It's not happening now because everybody's focusing on getting this thing under control.**

Ms. Brennan's suggestion of a 9/11 type commission and Dr. Fauci's concurrence never materialized. Dr. Fauci's analogy of an autopsy—which is, by the *autopsy's* very nature, a gross anatomic investigation of the <u>discreet, individually unique dead body</u> —falls far short of detailed analyses of > 1.1 million deaths in the aggregate.[30] Critical to the story-line of a fictional murder mystery in literature, the autopsy is an integral part of every murder investigation assisting in clarifying and elucidating the **Means**, **Motive**, and **Opportunity** of any alleged perpetrator.[53] While the coronavirus SARS-CoV-2 causing the viral disease COVID-19 is a non-sentient entity, from late 2019 to the present, coronavirus SARS-CoV-2 has been the *teleological* **real-life viral murderer** of greater than 1.1 million infected individuals in the COVID-19 epidemic

of the United States of America. Thus, the coronavirus SARS-CoV-2 murderer had the **Means, Motive,** and **Opportunity** to ravage the people of the United States of America and the World:

Means: The Pathophysiology of the coronavirus SARS-CoV-2[55-61]:

1. Biochemical and physical characteristics of the virion:
    a. An enveloped, positive-sense, single-stranded RNA virus of ~30 kb
    b. A highly-communicable respiratory 80 – 120 nm in-size-viral-particle[62] which can traverse an N95 mask[63] 5% of the time (N95 means the mask will stop particles <300 nm in size 0.95 (95%) of the time)
    c. While only α and β genera (of the four coronavirus α, β, δ, and γ genuses) of coronaviruses infect mammals, human α coronavirus (as with 229E and NL63) are responsible for the common cold and croup, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 are classified β coronaviruses
    d. Angiotensin Converting Enzyme 2 (ACE2) of the cell is the functional receptor for subunits on the Spike protein of SARS-Cov-2 virion[64-69]
    e. Markedly increased annual mortality[70] of 0.69 % mortality increase / year past the age of ~fifty:
        0 – 45 years Mortality rate (y) = 0.0004 (x) – 0.0023 $r^2 = 0.80$
        46 – 90 years Mortality rate (y) = 0.0067 (x) – 0.2647 $r^2 = 0.80$
2. Life cycle of the virion:
    a. Attachment
    b. Penetration
    c. Biosynthesis
    d. Maturation
    e. Release
3. Epidemiology: Long-term persistence in the United States with an initial epidemic stage of ~3 years and a predictable endemic stage of 9 centuries by the analysis of the logarithmic decay of the initial herd immunity plot over time.[71-74]
4. Virion Darwinistic mutability[75] that sustains the virion by variability with resistance to previously acquired endogenous immunity by vaccination (Active Immunization) or previous contraction(s) of the disease.

Motive:

1. Infection of human hosts, highly-contagious respiratory spread, and infection of additional human hosts
2. Virion self-preservation / survival and continued Virion reproduction

Opportunity / (Impediments) for the VIRUS: For the coronavirus' ***ability to infect the individual patient, cause systemic disease, and result possibly in the infected individual patient's death***, the coronavirus SAR-CoV-2 has:

1. **Intrinsic Opportunities / (Impediments) FOR THE VIRUS murderer** within the individual patient:

    a. Opportunities for the VIRUS:

i. In 2020, novel to the human race meaning that the human race was *immunologically naïve* to the coronavirus, SARS-CoV-2 that caused COVID-19
ii. A highly communicable respiratory virus with a very small size (80 – 120 nm) and thus there is no absolute "antiviral" impermeable masks as N95 masks permit 5% of all particles <300 nm to traverse the mask.
iii. Attaches to the cell via the ACE2 receptor and affects the patient's intrinsic Immunologic system and the Renin-Angiotensin-Aldostone system (RAS):
    1. During viremia (0 to ~ 7 days) initially as a bilateral pneumonia and
    2. During the later phases of the severe systemic disease of cytokine cascade[76-78] (*treated with steroids*) and bradykinin storm (*no known treatment*)[64-69]
iv. Progression within 10 days of coronavirus SARS-CoV-2 infection to the later phases of the COVID-19 disease activation of the cytokine cascade and increase in bradykinin production prior to full systemic immunological development of Immunoglobulin G (IgG)[60]

b. Impediments to the VIRUS:
    i. Previous contraction/infection of coronavirus, SARS-CoV-2 with the individual patient's development of plasma cells to produce polyclonal antibodies to the specific coronavirus, SARS-Cov-2 variant or group of variants
    ii. The individual's immune system's development of endogenous immunoglobulins systemically:
        1. By contraction (infection of the individual) of COVID-19 and development of IgM, IgG, and IgA (IgA in the nasopharynx) to a specific variate.
        2. Prophylaxis of the entire population with mRNA vaccines to stimulate in each individual endogenous plasma cells producing monoclonal IgM and IgG antibodies only to a specific variant or variants

2. **Extrinsic Opportunities / (Impediments) FOR THE VIRUS MURDERER** from <u>outside</u> the individual patient:

a. Opportunities for the VIRUS:
    i. **Uniform LACK of Universal Provision by U.S. Medicine and the Federal Government (*de facto rationing and patient abandonment* to every infected untreated individual) with <u>Early</u> Treatment (<120 hours)** with antivirals and exogenous immunoglobulins: COVID-19 Convalescent Plasma, monoclonal antibodies, and monoclonal antibody cocktails

ii. A highly communicable respiratory virus with a very small size (80 – 120 nm) and thus there is no absolute "antiviral" impermeable masks as N95 masks permit 5% of all particles <300 nm to traverse the mask.
iii. Attaches to the cell of the infected patient via the ACE2 receptor and affects the Renin-Angiotensin-Aldostone system (RAS), e.g.: During viremia (0 to ~ 7 days) as a bilateral pneumonia and during the later phase of severe systemic disease of cytokine cascade and bradykinin storm
iv. Progression within 10 days of coronavirus SARS-CoV-2 infection to the later phases of the COVID-19 disease activation of the cytokine cascade and increase in bradykinin production prior to full systemic immunological development of Immunoglobulin G (IgG)
v. Development of resistance to the monoclonal antibodies and the electronic overwriting by FDA so all will be forgotten by history; and the discontinuation by the Pharmaceutical Industry of development of ongoing new monoclonal antibodies (and cocktails).
vi. Development of new variants resistant to the mRNA vaccines that have already been developed and implemented.
vii. **Research grant funding and inappropriate statistical methodologies of the FDA, the NIH, BARDA, etc.:**
    1. Requiring mandatory placebo-controlled Clinical Trials when case-control clinical trials would have sufficed) **–*That is UNETHICAL;***
    2. Publishing underpowered, skewed, statistically inappropriate "research" condoned by the FDA, the NIH, *The New England Journal of Medicine*, etc. **—*That is just plain STUPID*** e.g.: *SIREN C3PO clinical trial,* NIH NCT04355767
    3. the denial and uniform lack of implementation by the FDA and the NIH of adherence to the Right to Try Act (PL-115-176) – **THIS IS REPREHENSIBLE** for federal agencies to violate the intent of the law**!**
viii. **Pharmaceutical Industrial short-sightedness and corporate greed**
ix. **The partisan mentality pervasive in our society**
x. **The shear ignorance, meanness, immorality, etc. of the Trump administration**
xi. Ignorant, uncomprehensible "compromise" that denies foundational scientific knowledge / logic, e.g.: the Supreme Court rulings of January 13, 2022, regarding requiring mandatory masks and vaccinations is **TANTAMOUNT TO SPLITTING THE CHILD IN HALF as posed by Solomon (1 Kings 3:16-28)**:
https://rollcall.com/2022/01/13/supreme-court-blocks-vaccine-or-mask-mandate-for-larger-employers/ ,
https://s3.documentcloud.org/documents/21178592/21a244-21a247.pdf ,
https://s3.documentcloud.org/documents/21178591/21a240-21a241.pdf , and
https://www.biblegateway.com/passage/?search=1%20Kings%203%3A16-28&version=CEV and
https://reason.com/2018/01/20/split-the-baby-drink-the-poiso/ .

b. Impediments to the VIRUS:
    i. Early **treatment (0 – 120 hours from diagnosis of the disease) with:**

1. Endogenous Immunoglobulins (Passive Immunization):
    a. COVID-19 Convalescent Plasma – If given within 72 – 120 hours, is effective, e.g.: https://www.nejm.org/doi/full/10.1056/nejmoa2031893
    b. Monoclonal Antibodies and monoclonal antibody cocktails **(the new variants of SARS-CoV-2 became resistant to the exogenous antibodies and the FDA has covered this up by electronic overwriting:**
2. Antivirals
    a. VEKLURY (Remdesivir) NDA 214787, [a nucleotide prodrug of an adenosine which binds to the viral RNA dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely.], is **the only FDA approved antiviral** against COVID-19;

        This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY(remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf

    b. PAXLOVID (nirmatrelvir [a SARS-CoV-2 main protease (Mpro) inhibitor (also known as SARS-CoV2 3CL protease inhibitor)] —and co-packaged with ritonavir [a cytochrome P450) CYP) 3A inhibitor is a protease inhibitor to prolong nirmatrelvir]) EUA 105 (last FDA overwriting of EUA 105 of 2/1/2023: https://www.fda.gov/media/155049/download ; initial FDA EUA of 12/22/2021: https://web.archive.org/web/20211222200348/https://www.fda.gov/media/155049/download)

    c. LAGEVRIO (molnupiravir [a ribonucleoside that is uptaken by viral RNA-dependent RNA-polymerases resulting viral mutations and viral mutagenesis]) EUA 108 (last FDA overwriting of EUA 108 of 2/1/2023: https://www.fda.gov/media/155053/download ; initial FDA EUA of 12/23/2021: https://web.archive.org/web/20211223201214/https://www.fda.gov/media/155053/download)

3. Steroids (like dexamethasone) in the suppression of the overactivation of the infected individual's immune system resulting in a cytokine cascade

4. There is no treatment for increasing bradykinin levels

While the **Means, Motives,** and **Intrinsic Opportunities** are consistent with the very nature and *modus operandi* of this **Viral Murderer**, **Coronavirus, SARS-CoV-2,** the:

1. **Extrinsic Opportunities** of this **Viral Murderer** have been accentuated, promoted, and enhanced inadvertently by American Societal prejudices, indifference, ignorance, and misinformation; and

2. **Extrinsic Impediments** of this **Viral Murderer** have been:

    a. minimized, provisionally addressed in a disorganized and chaotic fashion, and overall hidden from public unawareness;
    b. obfuscated, disregarded and dismissed by Medical Research, the Pharmaceutical industry, and Business magnified by their accentuation of their conflict-of-interests;
    c. magnified by the attitude of: *The End Justifies the Means;*
    d. exentuated by Personal Greed equated to professional and financial success;
    e. and general witlessness and resultant lack of individual scrutiny and analysis promoted by:
        i. overall American societal scientific illiteracy,
        ii. publicly accepted disregard for history,
        iii. dishonest and destructive overshadowing by political partisanism,
        iv. and just plain selfishness and meanness.

The story of the world-wide COVID-19 Pandemic in the United States of America is a national American epidemic tragedy imprinted forever in history and unfortunately, by the overall lack of early (<72 hours) uniform treatment response with exogenous immunoglobulins and antivirals, has become a commentary of man's stupidity and inhumanity towards his fellowman in this new millennium of the 21st Century.

Methods:

From April 2020 to the present (March 2023), the World literature--scientific, business parochial, and daily media—were perused, collected, recorded electronically, much were hard-copy filed--and over time three composite documents were submitted for preservation for history to the U.S. Copyright Office of the U.S. Library of Congress. From April 2020, analysis letters were composed and mailed to divisions of the U.S. Department of Health and Human Services (e.g.: FDA, NIAID , etc.), U.S. Department of Veterans Affairs (VA), and *The White House*. **The first submission to the U.S. Copyright Office in June 2020 was addressed by the NIAID Communications Officer at the direction of Dr. Fauci establishing a case number: NIH NIAID #12276 and *The White House* press secretary acknowledge the COVID-19 convalescent plasma "issue" in the Friday afternoon press conference of June 19, 2020**.

> …Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging…

The establishment of NIH NIAID Case File# 12276 became crucial to the continued official accumulation of data for this report going forward as by U.S. Federal Law **all** must be preserved and is discoverable through a formal request submitted to the NIAID FIOA officer. Confirmation of all documentation to the NIAID Director's Office (Anthony Fauci, M.D.) of ongoing continued preservation by the NIAID's Communications Officer's Office came in a form of a phone call over a year later on August 30, 2021, between Dr. Andrus and "Meg" on behalf of the office of Kara Harris, MPH, National Institute of Allergy and Infectious Diseases Communications and Liaison Officer, U.S. National Institutes of Health (NIH).

Case Report of the Chronology of the Treatment of Presidents Trump and Biden:

In October 2020, [which was prior to any vaccine (***Active Immunization)***], the unvaccinated individuals of Rudy Giuliani, Chris Christy, Ben Carson, M.D., and President Donald Trump contracted COVID-19. Immediately, within 72 hours of diagnosis, all four were treated with a monoclonal antibody or cocktail and the antiviral remdesivir (a 5 day course) and all survived. https://www.nytimes.com/2020/12/10/opinion/coronavirus-giuliani-regeneron.html

Reportedly, President Trump received Regeneron's monoclonal antibody cocktail within ~4 hours of diagnosis (***Passive Immunization***), a multiple day course of the antiviral remdesivir (I.V. bid) was initiated within 18 hours, and dexamethasone was administered. In fact, after this treatment, President Trump bragged that he was cured! https://www.forbes.com/sites/roberthart/2020/10/08/while-trump-touts-cure-made-by-regeneron-its-ceo-is-a-member-of-trump-golf-club/?sh=347f188860c8

The Individual COVID-19 timelines of President Trump and President Biden were as follows:

President Trump:

October 2020:	Contracted COVID-19 and was immediately treated with *Passive Immunization* (Regeneron's monoclonal antibody cocktail), a five-day course of the I.V. antiviral remdesivir, and also I.V. dexamethasone
January 2021:	First vaccine inoculation
March 1, 2021:	Second vaccine inoculation
Fall 2021:	Received a vaccine booster

President Biden:

December 21, 2020:	First vaccine inoculation
January 11, 2021:	Second vaccine inoculation
September 27, 2021:	1st vaccine booster
March 30, 2022:	2nd vaccine booster
July 21, 2022:	Contracted COVID-19 and was treated with a five-day course of the oral antiviral Paxlovid
October 25, 2022:	3rd vaccine booster (new version)

Results: Both President Trump and President Biden contracted the SARS-CoV-2 virus, clinically initiating COVID-19 symptoms, in which visa-à-vis one was unvaccinated while the other was vaccinated having contracted the virus later in the timeline. Both were appropriately treated as all individuals of the entire nation and the world should have been treated. The combination of (1) the administration of exogenous immunoglobulins or the body's utilizing endogenous immunoglobulins post-vaccination and (2) an antiviral are synergistic and should be given within the first 72 hours after diagnosis. This should have been and should be the Medical Standard of Care in the United States today for every man, woman, and child who contracts COVID-19 regardless of vaccination status or concomitant illnesses (e.g.: hypertension, diabetes, obesity, history of smoking, etc.)

In October 2020, the physicians caring for President Trump at Walter Reed Military Medical Center, FDA and NIH experts, medical publications, news commentators, the media, and the general public had the general impression that this combination was strictly experimental and thus not for the rank-and-file American. WHAT A BUNCH OF MEDICAL HOGWASH! This is the crux of the problem and the FDA, the NIH, the PHS, the CDC, Academic Medicine, all of United States Medicine, and all of the Federal Government were complicit in promoting this HOGWASH. As the case report of this summary exemplifies, AMERICAN MEDICINE failed the American people.

1.) This occurred because from March 13, 2020, to the present, the United States has been in an official Public Health Emergency (PHE). On that day, Secretary Azar suspended parts of EMTALA retroactive to March 1, 2020, thus officially abridging some part of every American's rights guaranteed by EMTALA:

a. Stabilization
b. Diagnosis
c. Treatment / Appropriate Disposition

2.) The Biden administration has renewed the PHE and thus the EMTALA waivers on February 24, 2021 renewing them every 90 days until PL-118-3 was signed into law on April 10, 2023. In August of 2022, CMS stated that the waivers would terminate once the Public Health Emergency (PHE) was declared concluded. By the signing of PL-118-3 rescinding President Trump's Executive Order 9994 of March 13, 2020, the PHE is to be ended in the coming weeks. **The FDA and the NIH have <u>a big ETHICAL and PRACTICAL problem</u> since any drug or test, etc. designated as authorized (not FDA approved) under an EUA should by FDA (and NIH) policies and definitions revert to "Investigational" / "Experimental."**

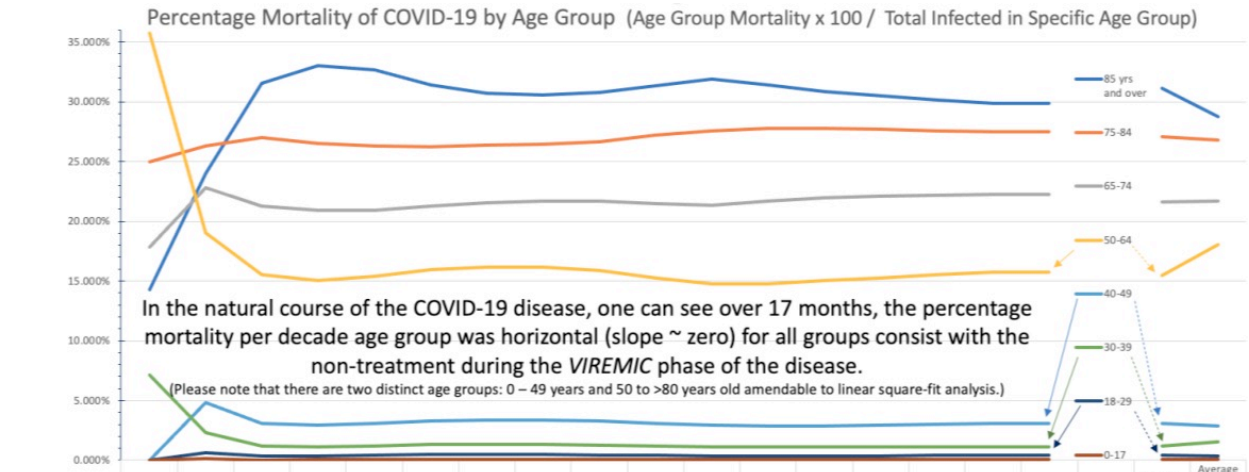
3.) In 2018, The Right to Tray Act became a Federal Law, PL-115-176, which stated that as soon an experimental drug or biologic has completed a Phase I (Safety) Clinical Trial, any American could request off-protocol the experimental/investigational drug or biologic for their personal use in the treatment of their specific disease. Through the ambiguity of euphemisms (Authorized versus Approved), the FDA and the NIH have facilitated through the use of the *Emergency Use Authorization* (**EUA**) that no antiviral except VEKLURY remdesivir nor biologic except the mRNA Pfizer and Moderna vaccines became prescription drugs. All other Immunoglobulins and Antivirals to treat COVID-19 and the Vaccines to prevent and provide prophylaxis against COVID-19 retained their "Experimental status"

under the EUAs. In short, the FDA has not officially declared all other drugs in the treatment of COVID-19 "SAFE" through a completed Phase I study thus flagrantly avoided application of the Right to Try Act of 2018 (PL-115-176) by not officially declaring Phase I Clinical Trials "ever being completed."

4.) While VEKLURY (remdesivir) is the only antiviral FDA approved in the treatment of COVID-19, the U.S. Government has promoted and provided through the Test and Treat Program under EUAs the oral Antivirals: Pfizer's Paxlovid and Merck's Lagevrio. Up until very recently, television advertisements for Pfizer's Paxlovid which is authorized under an FDA EUA but not FDA approved as a prescription antiviral did not mention the very name of the antiviral, Paxlovid, and legally still should not as it is "Investigational" under an FDA EUA. **Thus, a non-FDA-approved oral antiviral, Paxloid, is being marketed in deference to its competition with the intravenous antiviral VEKLURY (remdesivir), NDA 214787, which is a fully-FDA-Approved prescription drug.**

Discussion: During the initial year course of the disease of COVID-19 in the United States of America (USA) epidemic, early treatment (within 72 -120 hours of symptoms and diagnosis) with exogenous immunoglobulins (Passive Immunization—COVID-19 Convalescent Plasma) and the antiviral Remdesivir were *de facto* withheld from the vast majority of COVID-19 infected individuals in deference to the USA people waiting in anticipation for monoclonal antibodies, mRNA vaccines, and the oral antivirals which came a year or more later. The late-administration of treatment (>120 hours) or withholding completely of treatment with immunoglobulins and antivirals engendered by multiple divisions of the U.S. Department of Health and Human Services (e.g.: the FDA, the NIH, the NIH NIAID, PHS, etc.); the pharmaceutical and biologic industry, and *The White House* provided the opportunity to define the mortality of the natural course of untreated COVID-19 in a population by decades of life—very much akin to and analogous to the unethical Federal bureaucratic application of the Tuskegee Syphilis Project of the mid-twentieth century. The incidence of mortality attributable to COVID-19 in untreated or delayed treatment individuals by age-decade can be derived from the reports from the first year of the epidemic of the CDC which demonstrated a progressive age-related, mortality rate mathematically represented in Figures 1 & 2 and defined by two least-squared fits of:

0 – 45 years	Mortality rate (y) = 0.0004 (x) – 0.0023 $r^2 = 0.80$
46 – 90 years	Mortality rate (y) = 0.0067 (x) – 0.2647 $r^2 = 0.97$


Percentage Mortality of COVID-19 by Age Group (Age Group Mortality x 100 / Total Infected in Specific Age Group)
35.000%
30.000%
25.000%
20.000%
15.000%
10.000%
5.000%
0.000%
85 yrs and over
75-84
65-74
50-64
40-49
30-39
18-29
0-17
In the natural course of the COVID-19 disease, one can see over 17 months, the percentage mortality per decade age group was horizontal (slope ~ zero) for all groups consist with the non-treatment during the VIREMIC phase of the disease.
(Please note that there are two distinct age groups: 0 – 49 years and 50 to >80 years old amendable to linear square-fit analysis.)

	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-20201	May-21	Jun-21		Average from 4/2020 to present	Average from 1/2020 to the present
85 yrs and over	14.286%	23.964%	31.510%	33.007%	32.674%	31.398%	30.713%	30.536%	30.739%	31.324%	31.866%	31.378%	30.863%	30.484%	30.144%	29.874%	29.845%		31.090%	28.728%
75-84	25.000%	26.308%	26.972%	26.487%	26.277%	26.201%	26.335%	26.442%	26.671%	27.188%	27.571%	27.774%	27.779%	27.695%	27.569%	27.470%	27.463%		27.059%	26.789%
65-74	17.857%	22.763%	21.258%	20.921%	20.933%	21.276%	21.563%	21.675%	21.647%	21.472%	21.351%	21.663%	21.933%	22.098%	22.189%	22.264%	22.268%		21.634%	21.674%
50-64	35.714%	19.023%	15.528%	15.064%	15.367%	15.947%	16.148%	16.127%	15.857%	15.236%	14.728%	14.784%	15.019%	15.247%	15.517%	15.725%	15.750%		15.470%	18.016%
40-49	0.000%	4.843%	3.099%	2.964%	3.083%	3.318%	3.387%	3.376%	3.294%	3.098%	2.937%	2.885%	2.895%	2.944%	3.013%	3.065%	3.070%		3.095%	2.848%
30-39	7.143%	2.331%	1.218%	1.146%	1.216%	1.334%	1.327%	1.318%	1.282%	1.203%	1.111%	1.089%	1.085%	1.099%	1.125%	1.149%	1.149%		1.190%	1.518%
18-29	0.000%	0.656%	0.382%	0.369%	0.402%	0.469%	0.469%	0.467%	0.453%	0.421%	0.385%	0.376%	0.377%	0.382%	0.390%	0.399%	0.400%		0.409%	0.378%
0-17	0.000%	0.112%	0.034%	0.041%	0.048%	0.057%	0.058%	0.059%	0.059%	0.057%	0.051%	0.050%	0.050%	0.051%	0.053%	0.054%	0.055%		0.052%	0.049%

Figure 1: Y axis = monthly decade age group mortality due to COVID-19/total population of decade age group, Y axis = mortality rate in %. Data derived from the CDC database of sex and age mortality: https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge

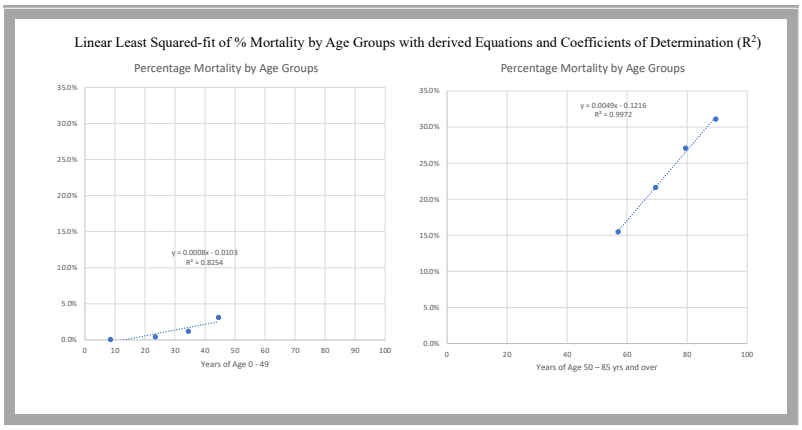

Linear Least Squared-fit of % Mortality by Age Groups with derived Equations and Coefficients of Determination (R^2)
Percentage Mortality by Age Groups
y = 0.0008x - 0.0103
R² = 0.8254
Years of Age 0 - 49
Percentage Mortality by Age Groups
y = 0.0049x - 0.1216
R² = 0.9972
Years of Age 50 – 85 yrs and over

Figure 2 is derived from a calculated least-squared fit of the data from Figure 1. The slopes x 100 equals the fraction increasing (0-45 years): 0.04 mortality annual increase / years and (45-90 years): 0.67 mortality annual increase / years, respectively. Thus, adult morality rate (45 years to 90 years) represents an increase of 0.67% mortality in each specific decade population per increasing year of life after 45 years of age.

Over the last 3 years, **two independent variables: TIME and AGE** stifled, inhibited, and promoted irrational rationing of **the appropriate treatment applications** in the vast majority of prospective Randomized Clinical Trials (RCT) COVID-19 treatment (not prophylaxis) studies as they were statistically underpowered (subject to Type II and Type III statistical errors); highly influenced by powerful research conflict-of-interest motivations; and misdirected and dismissed by egocentric financial and political incentives:

(1) **TIME: American Medicine and Research ignored the appropriate timing** of **Early (less than 120 hours from diagnosis) treatment in the administration TO ALL** of *exogenous immunoglobulins* and *antivirals* during the viremic phase of the disease. [Instead, most studies were conducted during the later human-organism-response phases after the initial 72-120 hour viremic phase:

a. Cytokine Cascade and

b. Bradykinin Storm which is resultant from the entry of the Coronavirus, SARS-CoV-2 via the angiotensin converting enzyme 2 (ACE-2) receptor as-well-as the virus's ACE/ACE2 balance disruption and the activation of the Renin-Angiotensin-Aldosterone-System (RAAS) resulting in increases in bradykinin]; and

(2) **AGE:** With the steep slope/increase in mortality rate with ages over 50 years (0.67% increased mortality/increasing age-year over 50 years of age), statistically very large comparative samples in all RCTs should have been employed to avoid a Type II error. A type II error is the assertion of a negative result from too-small-of-sample-sizes thus asserting equivalency of two comparison groups (**ß** risk) when the two groups may actually be statistically different. Due to difficulty in recruitment in treatment RCT COVID-19 studies in which placebo controls were used, most, if not all, of the multitude RCTs enrolled in the U.S. National Library of Medicine *ClinicalTrials.gov* comparing treatment versus placebo **were severely underpowered and the stated results were**

useless. While the medically-statistical-accepted **alpha** (p=0.05, a 95% confidence level) regarding mortality were not met in most of these studies, an appropriate **beta (ß)** (0.20) was never met in the RCTs and thus announcing negative results as definitive—as was consistently done--**were fallacious.** (e.g.: Argentine study, Prism study, etc.) While the Mayo Clinic / FDA COVID-19 **Expanded Access** *(FDA euphemism for Compassionate Use)* Protocol had a large number of COVID-19 Convalescent Plasma units (>94,000 patients treated) administered late **at the WRONG TIME (during the cytokine cascade and bradykinin storm) over the expanse of >50 - 90 years-of-age to 90 years)**, the 94,000 were not *de facto* eligible for any research as to the Protocol's ***Compassionate Use*** **status** as the World Health Organization and the U.S. Institute of Medicine previously had forewarned regarding Ebola.

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> Type I and type II errors are the two classic pitfalls in statistical analysis: finding a difference when there is none (type I) and failure to find a true difference (type II). **There is, in addition, another important error that regularly appears in scientific journals. This error, *the type III***

> ***error*,[1] occurs whenever the conclusions drawn are not supported by the data presented. In recent years, type III errors have been increasing in prevalence.** Some illustrations drawn from recently published articles should serve to define my point. I have deliberately omitted citation of sources because my intent is to illustrate, not embarrass.

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ATTACHMENT VI: Face page for *Reductio ad Absurdum:* The COVID-19 Tale of Two Presidents. The draft of this incomplete article can be found in reference 11: Andrus CH: *Book 4: Biden Response to The Summary of Book 1 COVID 19 And Where We Went Wrong*. Internet Archive, Uploaded 2024 Feb 05, pages e31-e130 of e848. https://archive.org/details/0.4-book-4-biden-response-to-the-summary-of-book-1-covid-19-and-where-we-went-wrong-2nd-attemp *** NIH NIAID Case #12276

Reductio ad Absurdum:[1]
The COVID-19 Tale of Two Presidents, the Ramifications of Fifty Years of American Scandal, Therapeutic Nihilism, and Medical Stupidity:

Euphemisms[239]**:** Experimental / Investigational / EUA,
Expanded Access / Compassionate Care
FDA Authorization vs FDA Approval,
Treatment vs Prophylaxis,
Active Immunization vs Passive Immunization, etc.,

FDA Archiving reliance on non-governmental sites

FDA archived web material is maintained within the Pagefreezer platform.

and loss of information by ***electronic overwriting*** and ***destruction*** of URLs,

FDA and NIH blatant, total disregard of the Right to Try Act (PL-115-176) by never declaring a completed Phase 1(Safety) [vs Phase 2/3 Efficacy] Clinical Trial and thus dismissing and *de facto* legally violating PL-115-176

Statistical Misdirection,

Predatory Marketing, and

> 1.1 million Americans dead associated with **withholding early** (**within 72-120 hours** of diagnosis) synergistic treatment with **Exogenous Immunoglobulins (Passive Immunization)** and **Antivirals**

Contingent on: Ignorance, Sins of Ommission, Conflicts-of-Interest, Greed

"Reform must come from within, not from without. You cannot legislate for Virtue" James Cardinal Gibbons, "Prince of Democracy"

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>
> > **(3) Level 3.** The staff practitioner is immediately available in the facility – campus for direct resident supervision according to local policy as approved by the Network Academic Affiliations Officer. The service chief is responsible for periodically reviewing cases done under Level 3 supervision to ensure that such supervision is appropriate.
>
> Using the Wayback Machine another version of the Level 3 Supervision (now Level D) is identified: In VHA Handbook of July 27, 2005 signed by Jonathan B. Perlin, M.D. https://web.archive.org/web/20051107072236/http:/www.va.gov:80/OAA/1400_1hk_July27_05.doc (Recission of the previous version of May 3, 2004 which cannot be found):
>
> > 4. **Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and immediately available for resident supervision or consultation as needed.

Using the only other "hit" on the Wayback Machine of December 21, 2016, http://web.archive.org/web/20161221045318/http://www.va.gov/oaa/1400_1hk_Oct2001.doc VHA 1400.1 has been removed completely and in its place is the website of the U.S. Department of Veterans Affairs which states: "Page Not Found." ***De facto*, the U.S. DVA, VHA**

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> **5. RECISSIONS.** VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005 is rescinded……. (page 1). [***Please note that when one searches for VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005, one is redirected to VHA Handbook 1400.01. Using the Wayback Machine and the previous URL for VHA 1400: http://web.archive.org/web/20161221045318/https://www.va.gov/oaa/1400_1hk_Oct2001.doc , one can find the 2001 version in the 2004 of the Internet Archive captures. There are no other captures of this URL in the Wayback Machine except December 21, 2016 which brings up the VA Website which states: "Page Not Found."***
>
> **4. Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and able to provide direct supervision or consultation without delay as needed. (page 9)

39. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063, Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. The original version of VHA Directive 1063 of December 24, 2013 which claimed physician assistants could be independent practitioners -- which I would allege is a violation of every State Medical Boards' credentialling policies/laws regarding Physician Assistants. In the 2013 version, the justification of the violation of all State Medical Boards was in 2.c:

> Under the Supremacy Clause of the U.S. Constitution, States are prohibited from regulating or controlling the activities of the Federal Government without written Congressional consent; where Federal and State laws conflict, Federal law governs official actions of Federal employees. Examples of the types of activities that the Federal Government may establish are qualifications for employment and scopes of practice. Therefore, the establishment of scopes of practice for VA PAs defined by this Directive is without regard to State Practice Acts.
> https://web.archive.org/web/20140814150238/https:/www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958

40. Petzel RA: Utilization of Physician Assistants (PA), VHA Directive 1063 (1), Veterans Health Administration, U.S. Department of Veterans Affairs, December 24, 2013. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2958 which is redirected when accessed to AMENDED June 24, 2024. Captured on July 22, 2023, by the *Internet Archive.* https://web.archive.org/web/20230722070741/https://www.va.gov/VHAPUBLICATIONS/ViewPublication.asp?pub_ID=2958 In **2. SUMMARY OF CHANGES** of the **Transmittal Sheet** which is still labelled **December 24, 2013** but in red has stamped: **AMENDED May 17, 2022** is: (1) Paragraphs 2.c. and 2.e. removes references to the Supremacy Clause reference and physician liability.—which means that the independent practice of a VHA Physician Assistant was rescinded returning all Physicians Assistants to the State Medical Board statutes outlining mandatory Physician scope of practice affiliations and legally mandated Physician oversight. The signatory official on this document is Robert A. Petzel, M.D., Under Secretary for Health who had been terminated over the Phoenix VAMC scandal 8 years prior to this as noted above in references 36 and 37.

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After OIG Inspector Griffin's testimony on May 8, 2003, ABC *Primetime* investigated for an entire year and on April 8, 2004, aired Fighting for Care narrated by Diane Sawyer. 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212) This episode was removed from the ABC Archives possibly because ABC to hidden cameras into the Cleveland and Temple, TX VAMCs. 2004 George Polk Award for "**Television Reporting: Diane Sawyer** and **Robbie Gordon**, ***ABC News PrimeTime Live***, for **"Fighting for Care,"** which documented patient abuse and deplorable conditions in VA hospitals." (for investigative reporting excellence) https://liu.edu/polk-awards/past-winners#2004. When Tammy Shehari, the Associate Producer for the episode, spoke with me by phone in 3/2004, she asked me to estimate how many additional veterans had died due to unsupervised operations performed by Surgery Residents– I declined to guess because to do so would be wrong and a disservice to the Veteran patients and the men and women of Department of Veterans Affairs that do their duty faithfully for Veteran patients. (The interview ended shortly after my refusing to guess, and this was the only time ABC News spoke with me.)

Please note the reference above -- VHA USH, Robert Roswell, M.D. resigned three days prior to the airing of *Fighting for Care*. *Fighting for Care* contained within unauthorized hidden cameras in the Cleveland VAMC and the Temple TX VAMC. The VA spin was: …Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. …. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

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> Antibodies have been used for a century for the prevention and treatment of infectious diseases (Table 1). In bacterial disease, antibodies neutralize toxins, facilitate opsonization, and, with complement, promote bacteriolysis; in viral disease, antibodies block viral entry into uninfected cells, promote antibody-directed cell-mediated cytotoxicity by natural killer cells, and neutralize virus alone or with the participation of complement.
>
> Prior to the use of antibiotics, antibodies were the only specific agents for the treatment of certain infections. Although this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1). Since several excellent reviews are available, this article will emphasize new developments (30, 31, 101, 164, 165).
>
> Antibodies can be administered as human or animal plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or convalescing donors, and as monoclonal antibodies (Mab) (30, 164,178). The therapeutic use of Mab is increasing dramatically, but only one (palivizumab for respiratory syncytial virus [RSV]) has been licensed for prophylaxis of an infectious disease.

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Footnote at bottom of every page of this Annotated Bibliographic Timeline:

---------- May 30, 2022 ---------- 3

This is a COVID-19 Timeline Bibliography for Educational Purposes *ONLY* in the presentation of this information before the people of the United States of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

This submission is NOT for financial gain but for educational purposes only for ALL the American people

0.7 Attachment VI Reductio ad Absurdum -- face sheet and references only.docx

0.7 Attachment VI Reductio ad Absurdum -- face sheet and references only.docx

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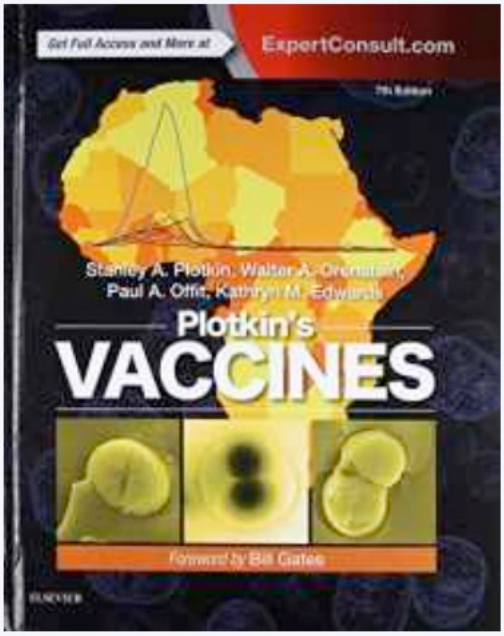
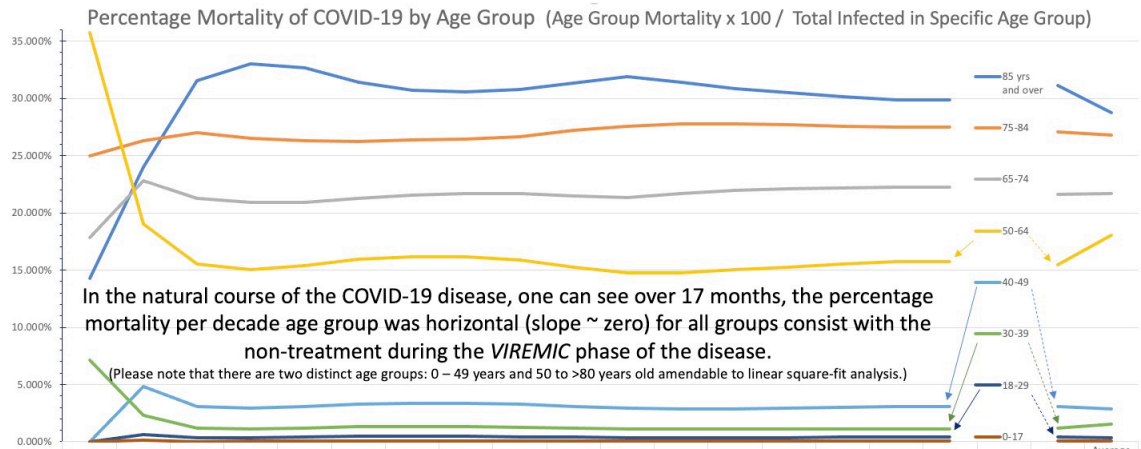
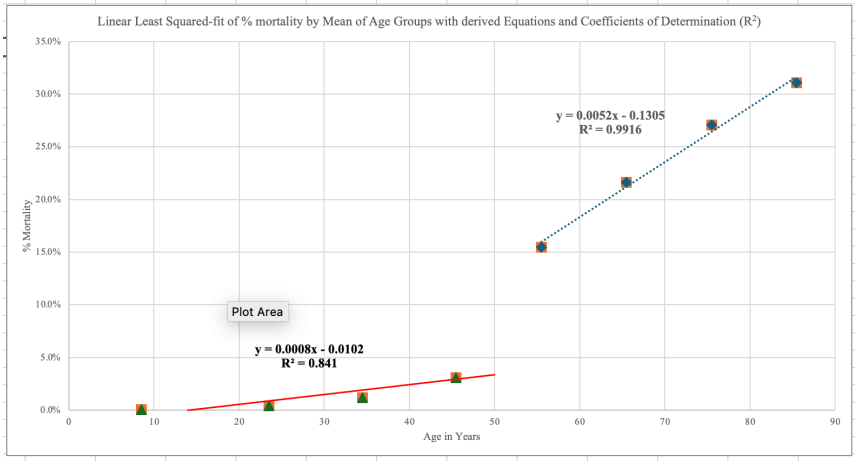


Graph IV, fig 1 and fig 2: Plots of Monthly Percentage Mortality from February 2020 to June 2021 reports of the CDC database of sex and mortality of COVID-19.[187]


Percentage Mortality of COVID-19 by Age Group (Age Group Mortality x 100 / Total Infected in Specific Age Group)
35.000%
30.000%
25.000%
20.000%
15.000%
10.000%
5.000%
0.000%
85 yrs and over
75-84
65-74
50-64
40-49
30-39
18-29
0-17
In the natural course of the COVID-19 disease, one can see over 17 months, the percentage mortality per decade age group was horizontal (slope ~ zero) for all groups consist with the non-treatment during the VIREMIC phase of the disease.
(Please note that there are two distinct age groups: 0 – 49 years and 50 to >80 years old amendable to linear square-fit analysis.)

	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-20201	May-21	Jun-21	Average from 4/2020 to present	Average from 1/2020 to the present
85 yrs and over	14.286%	23.964%	31.510%	33.007%	32.674%	31.398%	30.713%	30.536%	30.739%	31.324%	31.866%	31.378%	30.863%	30.484%	30.144%	29.874%	29.845%	31.090%	28.728%
75-84	25.000%	26.308%	26.972%	26.487%	26.277%	26.201%	26.335%	26.442%	26.671%	27.188%	27.571%	27.774%	27.779%	27.695%	27.569%	27.470%	27.463%	27.059%	26.789%
65-74	17.857%	22.763%	21.258%	20.921%	20.933%	21.276%	21.563%	21.675%	21.647%	21.472%	21.351%	21.663%	21.933%	22.098%	22.189%	22.264%	22.268%	21.634%	21.674%
50-64	35.714%	19.023%	15.528%	15.064%	15.367%	15.947%	16.148%	16.127%	15.857%	15.236%	14.728%	14.784%	15.019%	15.247%	15.517%	15.725%	15.750%	15.470%	18.016%
40-49	0.000%	4.843%	3.099%	2.964%	3.083%	3.318%	3.387%	3.376%	3.294%	3.098%	2.937%	2.885%	2.895%	2.944%	3.013%	3.065%	3.070%	3.095%	2.848%
30-39	7.143%	2.331%	1.218%	1.146%	1.216%	1.334%	1.327%	1.318%	1.282%	1.203%	1.111%	1.089%	1.085%	1.099%	1.125%	1.149%	1.149%	1.190%	1.518%
18-29	0.000%	0.656%	0.382%	0.369%	0.402%	0.469%	0.469%	0.467%	0.453%	0.421%	0.385%	0.376%	0.377%	0.382%	0.390%	0.399%	0.400%	0.409%	0.378%
0-17	0.000%	0.112%	0.034%	0.041%	0.048%	0.057%	0.058%	0.059%	0.059%	0.057%	0.051%	0.050%	0.050%	0.051%	0.053%	0.054%	0.055%	0.052%	0.049%

Fig 1: Y axis = monthly decade age group mortality due to COVID-19 total population of decade age group, Y axis = mortality rate in %. Data derived from the CDC database of sex and age mortality.
https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge [187]


Linear Least Squared-fit of % mortality by Mean of Age Groups with derived Equations and Coefficients of Determination (R²)
% Mortality
Age in Years
y = 0.0052x - 0.1305
R² = 0.9916
y = 0.0008x - 0.0102
R² = 0.841
Plot Area

0 – 49 years of age: Mortality rate (y) = 0.0008 (x) – 0.0102 $r^2 = 0.84$

50 – 90+ years of age: Mortality rate (y) = 0.0052 (x) – 0.1305 $r^2 = 0.99$

Fig 2 is derived from a calculated least-square fit of the data from Fig. 1. The slopes of the plots x 100 equals the fractional increase in mortality rate per year for the 0 – 49 age group of roughly 0.08% increase per age-year of the annual mortality and for the ≥50 age mortality of 0.52% increase per age-year of the annual mortality of ages are: 50 years of age, the calculated risk of mortality rate is: [(0.0052 x 50)-0.1305= 14%; 60 years of age, the calculated risk of mortality rate is: [(0.0052 x 60)-0.1305] = 18.2%; and 70 years of age, the calculated risk of mortality rate is [(0.0052 x 70)-0.1305]= 23.4%.

0.9 Attachment VIII_Pg 24_Graph IV from Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals.docx

0.9 Attachment VIII_Pg 24_Graph IV from Generalized Dismissal of Early Treatment with Passive Immunization and Antivirals.docx

Recommendation for using GamaSTAN S/D against measles for those exposed to measles who are undervaccinated, not vaccinated, or immunocompromised

From: Candrus600 (candrus600@aol.com)

To: surgeongeneral@hhs.gov

Cc: candrus600@aol.com

Date: Monday, March 24, 2025 at 03:55 PM CDT

3/24/2025

NIH NIAID Case #12276

Denis Hinton, MS, RN, FAAN
U.S. Deputy Surgeon General
Office of the Surgeon General
U.S. Department of Health and Human Services
200 Independence Ave SW
Humphrey Bldg, Suite 701H
Washington, DC 20201
surgeongeneral@hhs.gov
202-401-7529

Re: Using GamaSTAN S/D for those exposed to measles (Rubeola) and not adequately vaccinated

Dear Rear Admiral Hinton:

I am writing you today to suggest that as you are the acting Surgeon General at present, that you read the attached file which is a compressed .pdf file of that which I sent to DHHS Secretary Kennedy last Saturday, 3/22/2025. Since 1944, GamaSTAN has been FDA approved for post exposure prophylaxis (PEP) for all non-vaccinated, under vaccinated, or immunocompromised individuals who have been exposed to measles (Rubeola) to be administered within 6 days of exposure. As with other viruses in individuals post exposure or early during the viremic phase of the disease, *Passive Immunization* is indicated as an immunologic treatment with exogenous IgG. You may recall my correspondence with you regarding COVID-19 Convalescent Plasma when you were the FDA Chief Scientist. https://archive.org/details/book-1-dr-mr-president..-covid-19-and-where-we-went-wrong-2023-02-02/mode/2up [copy and paste into your search engine or through the advance search of the Internet Archive--put VA in the first field and Charles Andrus in the third (creator) field.] Please read the attachment to this e-mail (the letter is 12 pages)--for by passive immunization with GamaSTAN and then MMR 5 months later, the Prophylactic suppression success rate reported in the literature over the last 12 years against measles in individuals so treated is reportedly 99%. In is the recommended standard of care by the state public health services (CA, MN, NY, etc.) and the Canadian CDC (CCDC) and the Canadian provincial public health services. Thank you for considering this e-mail.

Respectfully,

Charles Andrus, M.D., F.A.C.S.
home phone: 314-455-9482

2025-3-21_Sec_Kennedy_ Immunizations_"Passive"-Treatment_vs_"Active"-Prophylaxis copy 2.pdf
20.8MB

A COVID-19 Treatment Timeline Bibliography: *Passive Immunization* and *Antiviral Agents*

1) 5000 B.C. Bennett M: First Commandment: You shall have no other gods. Exodus 20:3. *Life Hope & Truth*. https://lifehopeandtruth.com/bible/10-commandments/god-first-first-commandment/

2) 1599 Shakespeare: "…The play's the thing / Wherein I'll catch the conscience of the King." Hamlet, Act 2, Scene 2. https://www.enotes.com/homework-help/what-does-hamlet-mean-when-he-says-the-play-s-the-685602

3) 1776-07-04 Jefferson T: *Declaration of Independence*. U.S. National Archives. https://www.archives.gov/founding-docs/downloads?_ga=2.962417.190847131.1641315284-75845464.1641315284

4) 1776-09-22 America's Library: Patriot Hale was hanged September 22, 1776. http://www.americaslibrary.gov/jb/revolut/jb_revolut_hale_1.html

5) 1783 Madison J and the founders of the U.S.A.: The Constitution of the United States of America. https://www.archives.gov/founding-docs/constitution

> We the People of the United States, in Order to form a more perfect Union, establish Justice, insure domestic Tranquility, provide for the common defense, promote the general Welfare, and secure the Blessings of Liberty to. Ourselves and our Posterity, do ordain and establish this Constitution for the United States of America. https://www.archives.gov/founding-docs/constitution

6) 1787-07-06 Jefferson T: Letter from Thomas Jefferson to Thomas Mann Randolph, Jr., Paris July 6, 1787. U.S. National Archives. https://founders.archives.gov/documents/Jefferson/01-11-02-0475

> —but health, without which there is no happiness. An attention to health then should take place of every other object.

Constitutional Rights Foundation: Natural Rights: The Declaration of Independence and Natural Rights, Thomas Jefferson, drawing on the current thinking of his time, used natural rights ideas to justify declaring independence from England. (First written ~10/2008). https://www.crf-usa.org/foundations-of-our-constitution/natural-rights.html#:~:text=Most%20scholars%20today%20believe%20that,of%20English%20philosopher%20John%20Locke.&text=Among%20these%20fundamental%20natural%20rights,%2C%20liberty%2C%20and%20property.%22

7) 1837 Hans Christian Andersen: The Emperor's New Clothes. SDU, H.C. Andersen Centret. https://andersen.sdu.dk/vaerk/hersholt/TheEmperorsNewClothes_e.html

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8) 1865-03-04 Lincoln A: President Abraham Lincoln's Second Inaugural Address. OurDocuments https://www.ourdocuments.gov/doc.php?flash=false&doc=38

> *With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan—to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.*

9) 1865 Carroll, Lewis, (Charles Lutwidge Dogson) *Alice's Adventures in Wonderland*. London: MacMillan and Co., 1866. https://www.etsy.com/listing/1018008039/dodgson-charles-lutwidge-lewis-carroll?gpla=1&gao=1&&utm_source=google&utm_medium=cpc&utm_campaign=shopping_us_a-books_movies_and_music-books-childrens_books&utm_custom1=_k_EAIaIQobChMIwKjN_s2T9QIVAHNvBB1qWwZMEAQYAyABEgJqavD_BwE_k_&utm_content=go_12573073822_126376635984_507798475344_aud-1185363470307:pla-352609785060_c__1018008039_468327882&utm_custom2=12573073822&gclid=EAIaIQobChMIwKjN_s2T9QIVAHNvBB1qWwZMEAQYAyABEgJqavD_BwE

10) 1885 Twain M: First edition of the Adventures of Huckleberry Finn with an E.W. Kemble Illustration Laid In. New York: Charles L Webster and Company, 1885. (an early example of Twain's book.) https://www.raptisrarebooks.com/product/adventures-of-huckleberry-finn-mark-twain-first-edition-1885/

11) 1885-07-06 CDC: Historical perspectives a centennial celebration: Pasteur and the modern era of immunization. MMWR 9185 Jul 05; 34(26): 389-90. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000572.htm

12) 1873 Saxe JG: *The Blind Men and the Elephant*. This was a retelling by the American poet John Godrey Saxe of an Indian parable which epitomizes how individuals over the last several years with personal vested interests and self-promotion (e.g.: conflicts of interest to advance financial advancement, preserve the *status quo* with regards to research grants, misdirection of informed consents and continue coercion in research trials, etc.) have skewed the addressing of the COVID-19 pandemic for personal advancement. https://www.commonlit.org/en/texts/the-blind-men-and-the-elephant

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
Though all of them blind,
That each by observation
Might satisfy his mind.

The First approached the Elephant
And, happening to fall
Against his broad and sturhy side,
At once began to bawl:

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

"God bless me, but the Elephant
Is very like a wall!"

The Second, feeling the tusk
Cried, "Ho! What have we here
So very round and smooth and sharp?
To me 'tis very clear
This wonder of an Elephant
Is very like a spear!"

The Third approached the animal
And, happening to take
The squirming trunk within his hands,
Thus boldly up he spake:
"I see," quoth he, "The Elephant
Is very like a snake!"

The Fourth reached out an eager hand,
And felt about the knee:
"What most the wondrous beast is like
Is very plain," quoth he;
"Tis clear enough the Elephant
Is very like a tree!"

The Fifth, who chanced to touch the ear,
Said, "Even the blindest man
Can tell what this resembles most:
Deny the fact who can:
This marvel of an elephant
Is very like a fan!"

The Sixth no sooner had begun
About the beast to grope
Then, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the Elephant
Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong.

Though each was partly in right,
They all were in the wrong!

13) 1887 Acton: Lord Acton writes to Bishop Creighton that the same moral standards should be applied to all men, political and religious leaders included, especially since "Power tends to corrupt and absolute power corrupts absolutely." OLL https://oll.libertyfund.org/quote/lord-acton-writes-to-bishop-creighton-that-the-same-moral-standards-should-be-applied-to-all-

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men-political-and-religious-leaders-included-especially-since-power-tends-to-corrupt-and-absolute-power-corrupts-absolutely-1887

14) 1905 Santayana G: "Those who cannot remember the past are condemned to repeat it", *The Life of Reason, 1905.* From the series Great Ideas of Western Man. SAAM, Smithsonian American Art Museum. https://americanart.si.edu/artwork/those-who-cannot-remember-past-are-condemned-repeat-it-george-santayana-life-reason-1905

15) 1905 Robert E. Gross, M.D., born: Clatworthy HW: Robert E. Gross. https://pubmed.ncbi.nlm.nih.gov/3095885/ and https://fa.hms.harvard.edu/files/memorialminute_gross_robert_e.pdf

16) 1913 ACS: History of the American College of Surgeons. https://www.facs.org/about-acs/archives/acshistory

17) 1918-1919 CDC: History of the American College of Surgeons. https://www.facs.org/about-acs/acs-history/

18) 1926 de Kruif P: *Microbe Hunters*. New York: Harcourt, Brace, and Co., 1926. (New York: Paul de Kruif, Harcourt, Brace, Co., copyright renewed 1954). https://laurieximenez.files.wordpress.com/2016/03/2-microbe-hunters-paul-de-kruif.pdf

19) 1927-03-19 Peabody FW: The Care of the Patient. J Am Med Association. 1927 March 19; 88 (12): 877-882. (Presented at Boston Hospital, October 21, 1925). https://depts.washington.edu/medhmc/wordpress/wp-content/uploads/Peabody.html

20) 1933-03-04: Roosevelt FD: Inaugural Address of the President, Washington, D.C., March 4, 1933. https://www.archives.gov/files/education/lessons/fdr-inaugural/images/address-1.gif

> …So, first of all, let me assert my firm belief that the only thing we have to fear is fear itself – nameless, unreasoning, unjustified terror which paralyzes needed efforts to convert retreat to advances. In every dark hour of our national life a leadership of frankness and vigor has met with that understanding and support of the people themselves which is essential to victory. I am convinced that you will again give that support to leadership in these critical days.

21) 1937 Cronin AJ: *The Citadel*. Boston: Little, Brown & Co, 1937. Example: https://www.antiqbook.com/search.php?action=search&author=CRONIN%20%20&title=The%20Citadel

22) 1937 Farrow J: Damien the Leper. New York: Steel and Ward Inc., 1937. https://www.biblio.com/damien-the-leper-by-farrow-john/work/77302

23) 1939-10-19 Foster LR, Buchman S, Capra F: *Mr. Smith Goes to Washington*. Columbia Picture Corporation. https://www.dailyscript.com/scripts/MrSmithGoesToWashington.txt

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JEFFERSON
Just get up off the ground, that's all I ask. Get up there with that lady that is up on top of this Capitol dome--that lady that stands for liberty, take a look at this country through her eyes if you really want to see something and you won't just see scenery--you'll see the whole parade of what man's carved out for himself after centuries of fighting and fighting for something better than just jungle law, fighting he can stand on his own two feet-- free and decent, like he was created-- no matter what his race, color or creed. That's what you'll see. There's no place out there for graft or greed or lies or compromise with human liberties. And if that's what the grown-ups have done to this world that was given to them we'd better get those boy's camps started fast and see what the kids can do and it is not too late because this country is bigger than the Taylors, or you or me, or anything else. Great principles don't get lost once they come to light. They're right here. You just have to see them. …

JEFFERSON (with effort)
I guess this is just another lost cause, Mr. Paine. All you people don't know about lost causes. Mr. Paine does. He said once they were the only causes worth fighting for, and he fought for them once, for the only reason that any man ever fights for them. Because of just one plain, simple rule, "Love thy neighbor," and in this world today, full of hatred, a man who knows that one rule has a great trust. You knew that rule, Mr. Paine, and I loved you for it, just as my father did. And you know that you fight for the lost causes harder than for any others. Yes, you'd even die for them, like a man we both know, Mr. Paine. You think I'm licked. You all think I'm licked. Well, I'm not licked and I'm going to stay right here and fight for this lost cause even if this room gets filled with lies like these, and the Taylors and all their armies come marching into this place. Somebody'll listen to me--some-- …

24) 1940 DeAngelis CD (Former Editor-in-Chief, *Journal of the American Medical Association*): Biography. Changing the face of Medicine. https://cfmedicine.nlm.nih.gov/physicians/biography_77.html

25) 1942 Cronin AJ: *The Keys of the Kingdom*. Pub: Alfred Scherz Berne, 1942. https://www.abebooks.com/servlet/SearchResults?an=cronin&cm_sp=sort-_-SRP-_-Results&fe=on&sortby=1&tn=keys%20kingdom

26) 1944-06-25 Army Service Forces, Office of the Chief, Chemical Warfare Service, Gravelly Point, Washington, 25, D.C.

SPECIAL ORDERS) 25 June 1944
)
No. 152)

1. The Chief of Chemical Warfare Service commends the officers and enlisted men who voluntarily submitted to tests conducted by the Medical Division. These men participated beyond the call of duty by subjecting themselves to pain, discomfort, and possible permanent injury for the advancement of research in protection for our armed forces. Those named below knowingly submitted to exposure to chemical agents for some period during the months designated:

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September and October, 1943

PVT. EARL L. ALEXANDER, JR, 35704460
PVT. EDWARD A. ALTMAN, 33783419
PVT. CHARLES H. ANDRUS, JR, 1919066…

PVT. CHARLES H. ANDRUS, JR, 1919066 was the father of Charles H. Andrus, III, M.D., F.A.C.S. Obituary of Charles Hiram Andrus, Jr., April 30, 1921 – December 21, 2013
https://www.legacy.com/us/obituaries/sfgate/name/charles-andrus-obituary?id=17958880

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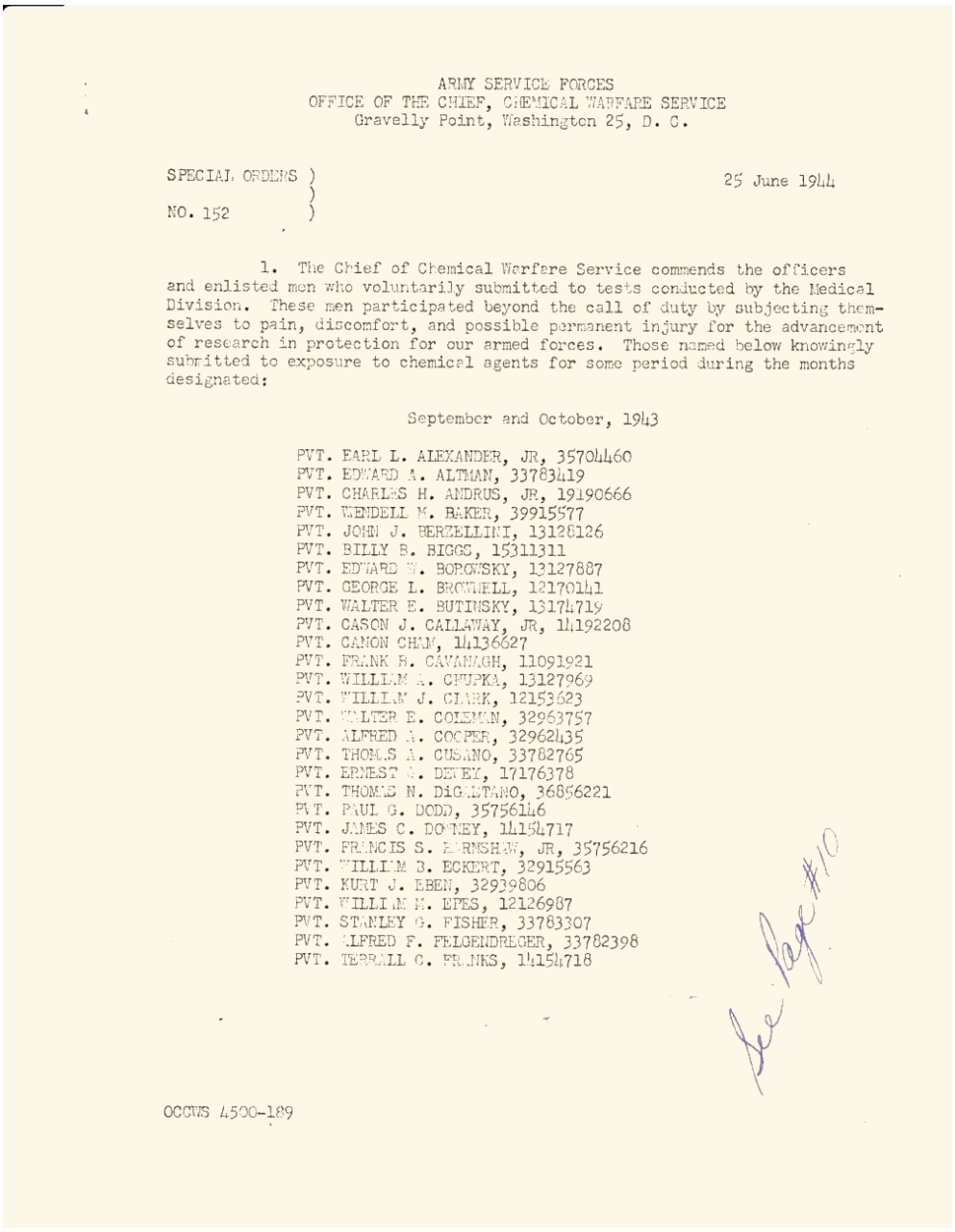

ARMY SERVICE FORCES
OFFICE OF THE CHIEF, CHEMICAL WARFARE SERVICE
Gravelly Point, Washington 25, D. C.

SPECIAL ORDERS)
)
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25 June 1944

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September and October, 1943

PVT. EARL L. ALEXANDER, JR, 35704460
PVT. EDWARD A. ALTMAN, 33783419
PVT. CHARLES H. ANDRUS, JR, 19190666
PVT. WENDELL M. BAKER, 39915577
PVT. JOHN J. BERZELLINI, 13128126
PVT. BILLY B. BIGGS, 15311311
PVT. EDWARD W. BOROWSKY, 13127887
PVT. GEORGE L. BROWNELL, 12170141
PVT. WALTER E. BUTINSKY, 13174719
PVT. CASON J. CALLAWAY, JR, 14192208
PVT. CANON CHAM, 14136627
PVT. FRANK B. CAVANAGH, 11091921
PVT. WILLIAM A. CHUPKA, 13127969
PVT. WILLIAM J. CLARK, 12153623
PVT. WALTER E. COLEMAN, 32963757
PVT. ALFRED A. COOPER, 32962435
PVT. THOMAS A. CUSANO, 33782765
PVT. ERNEST W. DEWEY, 17176378
PVT. THOMAS N. DiGAETANO, 36856221
PVT. PAUL G. DODD, 35756146
PVT. JAMES C. DOWNEY, 14154717
PVT. FRANCIS S. ERNSHAW, JR, 35756216
PVT. WILLIAM B. ECKERT, 32915563
PVT. KURT J. EBEN, 32939806
PVT. WILLIAM M. EPES, 12126987
PVT. STANLEY G. FISHER, 33783307
PVT. ALFRED F. FELGENDREGER, 33782398
PVT. TERRALL C. FRANKS, 14154718

See page #10

OCCWS 4500-189

From 2015-06-22 Dickerson C: Secret World War II Chemical Experiments Tested Troops By Race. (World War II Secret Mustard Gas Testing) NPR s|t|l|p|r June 22, 2015. https://www.npr.org/2015/06/22/415194765/u-s-troops-tested-by-race-in-secret-world-war-ii-chemical-experiments The original document above was the first page of a thirty-one page document that can be accessed by the hyperlink in the NPR document: Attached was a long list of names.

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27) 1944-10-25 Tillman B: The Gambier Bay's Final Hours. U.S. Naval Institute: Naval History Magazine 2019 Oct 33(5). https://www.usni.org/magazines/naval-history-magazine/2019/october/gambier-bays-final-hours

28) 1946 Orwell G: *Animal Farm* New York: Harcourt, Brace and Company, 1946. https://www.worldcat.org/title/animal-farm/oclc/366597

29) 1946-01-03 PL-79-293 authorizes the Department of Medicine and Surgery at the Veterans Administration. [2015-01-31We Served Too: VA history: VA's Department of Medicine and Surgery established. https://weservedtoo.wordpress.com/2015/01/31/va-history-vas-department-of-medicine-and-surgery-established/

30) 1946-01-31 U.S. Department of Veterans Administration: Memorandum No. 2: Policy in Association of Veterans, Hospitals with Medical Schools. https://www.va.gov/oaa/Archive/PolicyMemo2.pdf

31) 1948-12 Likert R: Public Opinion Polls. Why did they fail? A leading authority assays their weaknesses and suggests some tested new techniques that would improve their accuracy. Scientific American https://www.scientificamerican.com/article/public-opinion-polls/ (copy of article can be found in Scientific American.)

> Dr. Likert developed his scale of attitudes to more simply define the general differences in attitudes of any given population using a scale that though arbitrary, had to show internal consistency. The scaling method demonstrated in the original paper a value in revealing general differences shown by different groups towards any subject with which they have dealings ; thus revealing their tendencies only towards a particular response and not any specific measured result. Controversy surrounds the attempt to use statistical means to give more understanding to Likert scale data.
>
> The controversy involves the use of parametric analysis for ordinal data. As described by Likert originally, the numerical scale that is used in association with the arbitrary numbers of his scale of attitudes allows for the scale to be internally consistent. The scale also should appear to be based on equal seeming differences so when applied to a random population the validity is not placed in question. It is because of this number scale that parametric data can easily be used and which then raises the concern if you should apply parametric analysis to a number set obtained through ordinal means.
>
> Jamieson *et al.* (2004) reiterates that mean and mode should be used as a 'measure of central tendency' instead of mean and standard deviations as the later are inappropriate for ordinal data. There are non-parametric test that should be used simply because to use parametric analysis the data must be of interval or ratio level. Pell (2005) offers a different point that non-parametric analysis can be used given the 'assumptions are clearly stated and the data is of the appropriate size and shape.' He remarks that this analysis can provide useful insight but that caution should be exercised before arriving at statistical conclusions.
>
> Although sound data cannot honestly be obtained from parametric analysis of ordinal data, it is agreed in the literature that meaningful results and trends can be obtained and that even a combination of the two means may be used to greater results. –Author unknown to Dr. Andrus--

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32) 1949 Orwell G: *Nineteen Eighty-Four*. London: Secker & Warburg, 1949. http://wordsmith.org/words/unperson.html

33) 1951 Salinger JD: *The Catcher in the Rye.* Unknown date of a Study Guide by J.D. Salinger: *The Catcher in the Rye* Wisdom and Knowledge. https://www.shmoop.com/study-guides/literature/catcher-in-the-rye/quotes/wisdom-and-knowledge

> Holden Caulfield: "You ought to go to a boy's school sometime. Try it sometime," I said. "It's full of phonies, and all you do is study so that you can learn enough to be smart to be able to buy a goddam Cadillac some day, and you have to keep making believe you give a damn if the football team loses, and all you do is talk about girls and liquor and sex all day, and everybody sticks together in these dirty little goddam cliques."

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> …Those Kansas newspaper and political leaders who had bitterly denounced him in earlier years praised Ross for his stand against legislative mob rule: "By the firmness and courage of Senator Ross," it said, "the country was saved from calamity greater than war, while it consigned him to a political martyrdom, the most cruel in our history… Ross was the victim of a wild flame of intolerance which swept everything before it. He did his duty knowing that it meant his political death…It was a brave thing for Ross to do, but Ross did it. He acted for his conscience and with a lofty patriotism, regardless of what he knew must be the ruinous consequences to himself. He acted right."

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

> Gallantry in action. Intrepidity. Above and beyond call of duty. Risk of life. Selflessness. Exemplary action. Unwavering devotion. Conspicuous gallantry. Extraordinary heroism. The words enshrined with the Medal of Honor citations capture the best of what it means to be human.

41) 1958-09-20 Peirce ER, Melville FS, Downie AW, Duckworth MJ: Antivaccinial gamma-globulin in smallpox prophylaxis. The Lancet 1958 September 20: 272 (7047); 635-638. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(58)90351-9/fulltext ; https://www.sciencedirect.com/sdfe/pdf/download/eid/1-s2.0-S0140673658903519/first-page-pdf

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43) 1959-01 Gordon VH: The use of gamma globulin In Infectious Disease. J Ark Med Soc 1959 Jan; 55(8): 299-303. https://journals.sagepub.com/doi/pdf/10.1177/216507995900700407

44) 1959-07-11 Semple AB, Parry WH, Hobday TL: Antivaccinial gamma-globulin; a further report on smallpox prophylaxis. Lancet 1959 Jul 11; 2(7089): 34. https://pubmed.ncbi.nlm.nih.gov/13673585/

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> This paper records an attempt to assess the prophylactic value of immune gamma-globulin, prepared from the serum of recently vaccinated adults, in the protection of close contacts of smallpox in Madras. The results serve to confirm findings of a previous study made in Madas in 1953, and show that the incidence of smallpox in close contacts given immune gamma-globulin prophylactically was about a quarter of that in the control contacts who received no such passive immunization—a statistically significant difference. Because of the limited supply of immiune gamma-globulin, is likely that its prophylactic use will be restricted to those especially at risk, for example, close unvaccinated family contacts, newborn infants and pregnant women.

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Prevention: *Active Immunization*: Vaccines

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> It therefore seems that antivaccinial gamma-globulin can be an effective agent in the prevention of smallpox where contacts are detected too late for vaccination to afford protection; it can never supplant vaccination, but is complementary and may succeed where vaccination must fail.

53) 1963-06-10 Kennedy JF: Commencement Address at American University. https://www.jfklibrary.org/archives/other-resources/john-f-kennedy-speeches/american-university-19630610

> So, let us not be blind to our differences--but let us also direct attention to our common interests and to the means by which those differences can be resolved. And if we cannot end now our differences, at least we can help make the world safe for diversity. For, in the final analysis, our most basic common link is that we all inhabit this small planet. We all breathe the same air. We all cherish our children's future. And we are all mortal.

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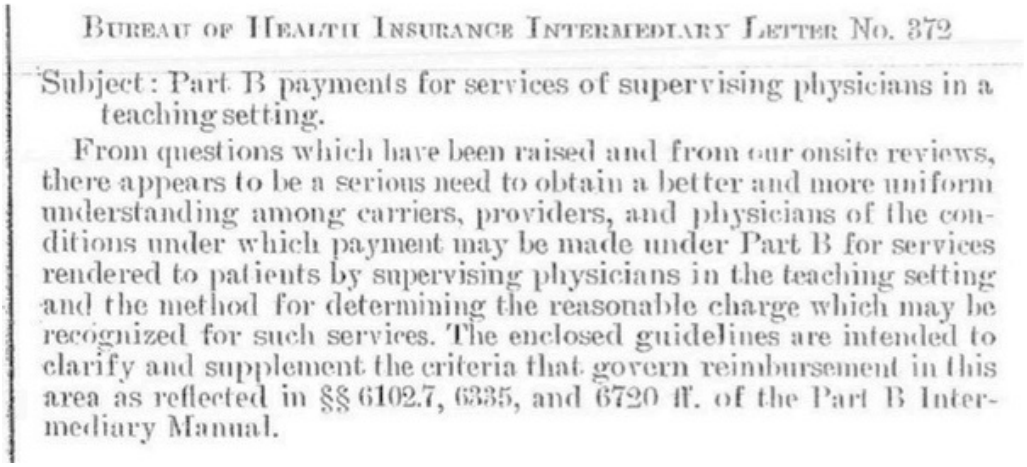

BUREAU OF HEALTH INSURANCE INTERMEDIARY LETTER NO. 372

Subject: Part B payments for services of supervising physicians in a teaching setting.

From questions which have been raised and from our onsite reviews, there appears to be a serious need to obtain a better and more uniform understanding among carriers, providers, and physicians of the conditions under which payment may be made under Part B for services rendered to patients by supervising physicians in the teaching setting and the method for determining the reasonable charge which may be recognized for such services. The enclosed guidelines are intended to clarify and supplement the criteria that govern reimbursement in this area as reflected in §§ 6102.7, 6335, and 6720 ff. of the Part B Intermediary Manual.

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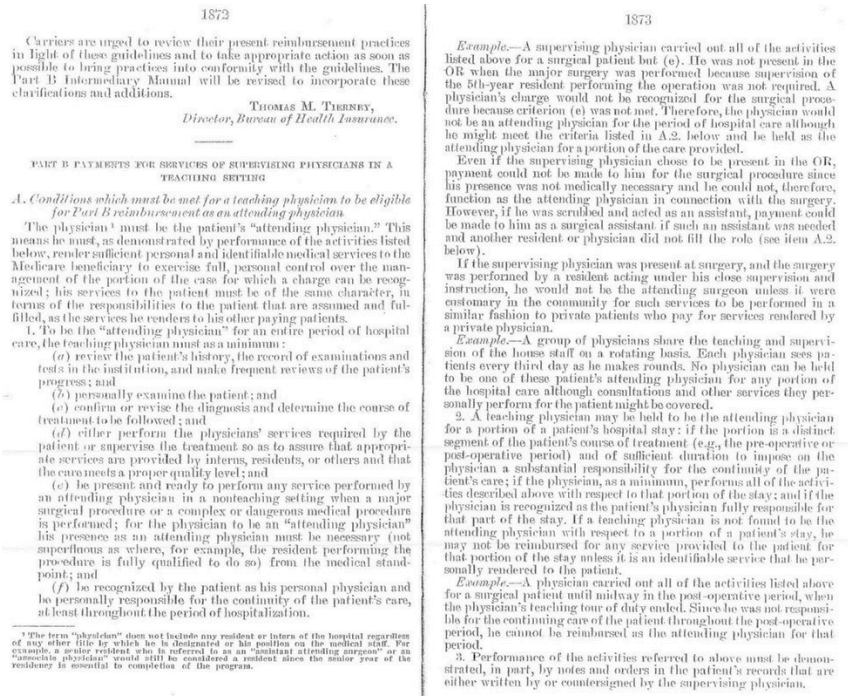

1872

Carriers are urged to review their present reimbursement practices in light of these guidelines and to take appropriate action as soon as possible to bring practices into conformity with the guidelines. The Part B Intermediary Manual will be revised to incorporate these clarifications and additions.

THOMAS M. TIERNEY,
Director, Bureau of Health Insurance.

PART B PAYMENTS FOR SERVICES OF SUPERVISING PHYSICIANS IN A TEACHING SETTING

A. Conditions which must be met for a teaching physician to be eligible for Part B reimbursement as an attending physician

The physician [1] must be the patient's "attending physician." This means he must, as demonstrated by performance of the activities listed below, render sufficient personal and identifiable medical services to the Medicare beneficiary to exercise full, personal control over the management of the portion of the case for which a charge can be recognized; his services to the patient must be of the same character, in terms of the responsibilities to the patient that are assumed and fulfilled, as the services he renders to his other paying patients.

1. To be the "attending physician" for an entire period of hospital care, the teaching physician must as a minimum:

(*a*) review the patient's history, the record of examinations and tests in the institution, and make frequent reviews of the patient's progress; and

(*b*) personally examine the patient; and

(*c*) confirm or revise the diagnosis and determine the course of treatment to be followed; and

(*d*) either perform the physicians' services required by the patient or supervise the treatment so as to assure that appropriate services are provided by interns, residents, or others and that the care meets a proper quality level; and

(*e*) be present and ready to perform any service performed by an attending physician in a nonteaching setting when a major surgical procedure or a complex or dangerous medical procedure is performed; for the physician to be an "attending physician" his presence as an attending physician must be necessary (not superfluous as where, for example, the resident performing the procedure is fully qualified to do so) from the medical standpoint; and

(*f*) be recognized by the patient as his personal physician and be personally responsible for the continuity of the patient's care, at least throughout the period of hospitalization.

[1] The term "physician" does not include any resident or intern of the hospital regardless of any other title by which he is designated or his position on the medical staff. For example, a senior resident who is referred to as an "assistant attending surgeon" or an "associate physician" would still be considered a resident since the senior year of the residency is essential to completion of the program.

1873

Example.—A supervising physician carried out all of the activities listed above for a surgical patient but (e). He was not present in the OR when the major surgery was performed because supervision of the 5th-year resident performing the operation was not required. A physician's charge would not be recognized for the surgical procedure because criterion (e) was not met. Therefore, the physician would not be an attending physician for the period of hospital care although he might meet the criteria listed in A.2. below and be held as the attending physician for a portion of the care provided.

Even if the supervising physician chose to be present in the OR, payment could not be made to him for the surgical procedure since his presence was not medically necessary and he could not, therefore, function as the attending physician in connection with the surgery. However, if he was scrubbed and acted as an assistant, payment could be made to him as a surgical assistant if such an assistant was needed and another resident or physician did not fill the role (see item A.2. below).

If the supervising physician was present at surgery, and the surgery was performed by a resident acting under his close supervision and instruction, he would not be the attending surgeon unless it were customary in the community for such services to be performed in a similar fashion to private patients who pay for services rendered by a private physician.

Example.—A group of physicians share the teaching and supervision of the house staff on a rotating basis. Each physician sees patients every third day as he makes rounds. No physician can be held to be one of these patient's attending physician for any portion of the hospital care although consultations and other services they personally perform for the patient might be covered.

2. A teaching physician may be held to be the attending physician for a portion of a patient's hospital stay: if the portion is a distinct segment of the patient's course of treatment (e.g., the pre-operative or post-operative period) and of sufficient duration to impose on the physician a substantial responsibility for the continuity of the patient's care; if the physician, as a minimum, performs all of the activities described above with respect to that portion of the stay; and if the physician is recognized as the patient's physician fully responsible for that part of the stay. If a teaching physician is not found to be the attending physician with respect to a portion of a patient's stay, he may not be reimbursed for any service provided to the patient for that portion of the stay unless it is an identifiable service that he personally rendered to the patient.

Example.—A physician carried out all of the activities listed above for a surgical patient until midway in the post-operative period, when the physician's teaching tour of duty ended. Since he was not responsible for the continuing care of the patient throughout the post-operative period, he cannot be reimbursed as the attending physician for that period.

3. Performance of the activities referred to above must be demonstrated, in part, by notes and orders in the patient's records that are either written by or countersigned by the supervising physician.

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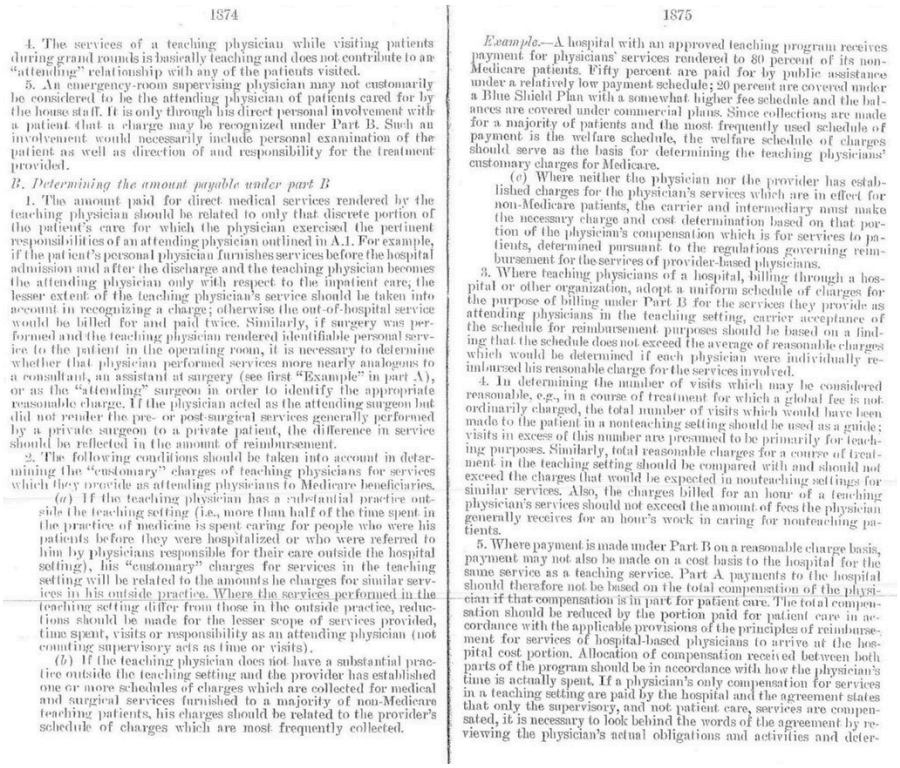

1874

4. The services of a teaching physician while visiting patients during grand rounds is basically teaching and does not contribute to an "attending" relationship with any of the patients visited.

5. An emergency-room supervising physician may not customarily be considered to be the attending physician of patients cared for by the house staff. It is only through his direct personal involvement with a patient that a charge may be recognized under Part B. Such an involvement would necessarily include personal examination of the patient as well as direction of and responsibility for the treatment provided.

B. Determining the amount payable under part B

1. The amount paid for direct medical services rendered by the teaching physician should be related to only that discrete portion of the patient's care for which the physician exercised the pertinent responsibilities of an attending physician outlined in A.1. For example, if the patient's personal physician furnishes services before the hospital admission and after the discharge and the teaching physician becomes the attending physician only with respect to the inpatient care, the lesser extent of the teaching physician's service should be taken into account in recognizing a charge; otherwise the out-of-hospital service would be billed for and paid twice. Similarly, if surgery was performed and the teaching physician rendered identifiable personal service to the patient in the operating room, it is necessary to determine whether that physician performed services more nearly analogous to a consultant, an assistant at surgery (see first "Example" in part A), or as the "attending" surgeon in order to identify the appropriate reasonable charge. If the physician acted as the attending surgeon but did not render the pre- or post-surgical services generally performed by a private surgeon to a private patient, the difference in service should be reflected in the amount of reimbursement.

2. The following conditions should be taken into account in determining the "customary" charges of teaching physicians for services which they provide as attending physicians to Medicare beneficiaries.

(*a*) If the teaching physician has a substantial practice outside the teaching setting (i.e., more than half of the time spent in the practice of medicine is spent caring for people who were his patients before they were hospitalized or who were referred to him by physicians responsible for their care outside the hospital setting), his "customary" charges for services in the teaching setting will be related to the amounts he charges for similar services in his outside practice. Where the services performed in the teaching setting differ from those in the outside practice, reductions should be made for the lesser scope of services provided, time spent, visits or responsibility as an attending physician (not counting supervisory acts as time or visits).

(*b*) If the teaching physician does not have a substantial practice outside the teaching setting and the provider has established one or more schedules of charges which are collected for medical and surgical services furnished to a majority of non-Medicare teaching patients, his charges should be related to the provider's schedule of charges which are most frequently collected.

1875

Example.—A hospital with an approved teaching program receives payment for physicians' services rendered to 80 percent of its non-Medicare patients. Fifty percent are paid for by public assistance under a relatively low payment schedule; 20 percent are covered under a Blue Shield Plan with a somewhat higher fee schedule and the balances are covered under commercial plans. Since collections are made for a majority of patients and the most frequently used schedule of payment is the welfare schedule, the welfare schedule of charges should serve as the basis for determining the teaching physicians' customary charges for Medicare.

(*c*) Where neither the physician nor the provider has established charges for the physician's services which are in effect for non-Medicare patients, the carrier and intermediary must make the necessary charge and cost determination based on that portion of the physician's compensation which is for services to patients, determined pursuant to the regulations governing reimbursement for the services of provider-based physicians.

3. Where teaching physicians of a hospital, billing through a hospital or other organization, adopt a uniform schedule of charges for the purpose of billing under Part B for the services they provide as attending physicians in the teaching setting, carrier acceptance of the schedule for reimbursement purposes should be based on a finding that the schedule does not exceed the average of reasonable charges which would be determined if each physician were individually reimbursed his reasonable charge for the services involved.

4. In determining the number of visits which may be considered reasonable, e.g., in a course of treatment for which a global fee is not ordinarily charged, the total number of visits which would have been made to the patient in a nonteaching setting should be used as a guide; visits in excess of this number are presumed to be primarily for teaching purposes. Similarly, total reasonable charges for a course of treatment in the teaching setting should be compared with and should not exceed the charges that would be expected in nonteaching settings for similar services. Also, the charges billed for an hour of a teaching physician's services should not exceed the amount of fees the physician generally receives for an hour's work in caring for nonteaching patients.

5. Where payment is made under Part B on a reasonable charge basis, payment may not also be made on a cost basis to the hospital for the same service as a teaching service. Part A payments to the hospital should therefore not be based on the total compensation of the physician if that compensation is in part for patient care. The total compensation should be reduced by the portion paid for patient care in accordance with the applicable provisions of the principles of reimbursement for services of hospital-based physicians to arrive at the hospital cost portion. Allocation of compensation received between both parts of the program should be in accordance with how the physician's time is actually spent. If a physician's only compensation for services in a teaching setting are paid by the hospital and the agreement states that only the supervisory, and not patient care, services are compensated, it is necessary to look behind the words of the agreement by reviewing the physician's actual obligations and activities and deter-

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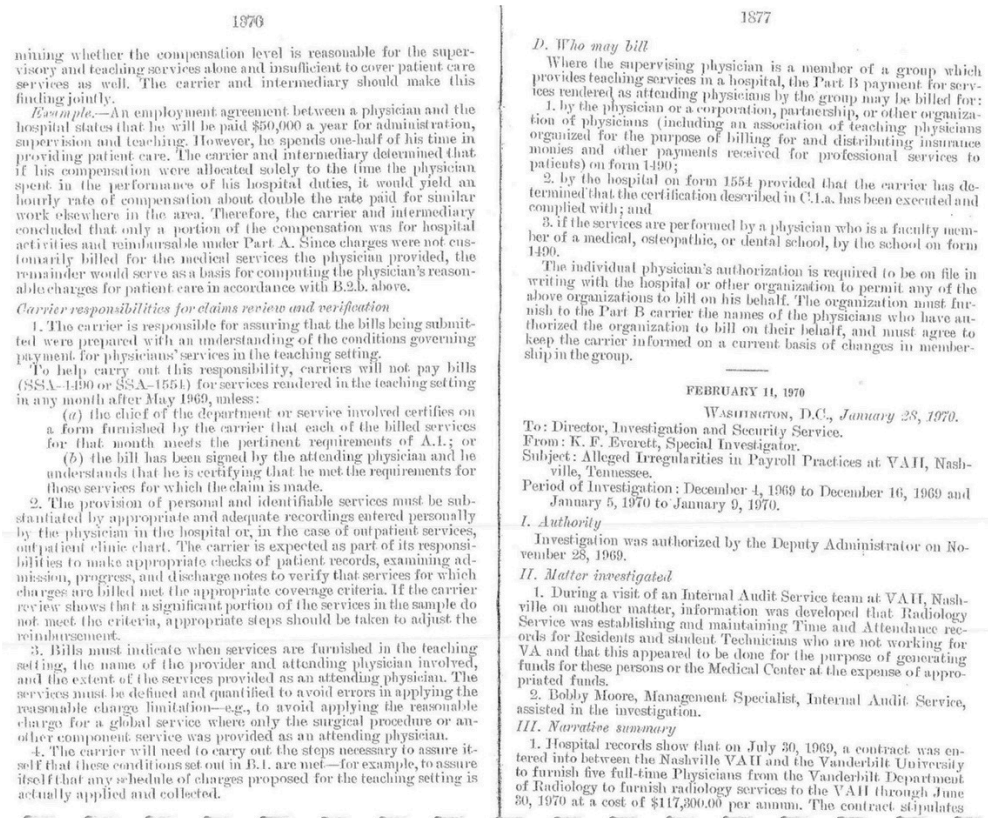

1870

mining whether the compensation level is reasonable for the supervisory and teaching services alone and insufficient to cover patient care services as well. The carrier and intermediary should make this finding jointly.

Example.—An employment agreement between a physician and the hospital states that he will be paid $50,000 a year for administration, supervision and teaching. However, he spends one-half of his time in providing patient care. The carrier and intermediary determined that if his compensation were allocated solely to the time the physician spent in the performance of his hospital duties, it would yield an hourly rate of compensation about double the rate paid for similar work elsewhere in the area. Therefore, the carrier and intermediary concluded that only a portion of the compensation was for hospital activities and reimbursable under Part A. Since charges were not customarily billed for the medical services the physician provided, the remainder would serve as a basis for computing the physician's reasonable charges for patient care in accordance with B.2.b. above.

Carrier responsibilities for claims review and verification

1. The carrier is responsible for assuring that the bills being submitted were prepared with an understanding of the conditions governing payment for physicians' services in the teaching setting.

To help carry out this responsibility, carriers will not pay bills (SSA–1490 or SSA–1554) for services rendered in the teaching setting in any month after May 1969, unless:

(*a*) the chief of the department or service involved certifies on a form furnished by the carrier that each of the billed services for that month meets the pertinent requirements of A.1.; or

(*b*) the bill has been signed by the attending physician and he understands that he is certifying that he met the requirements for those services for which the claim is made.

2. The provision of personal and identifiable services must be substantiated by appropriate and adequate recordings entered personally by the physician in the hospital or, in the case of outpatient services, outpatient clinic chart. The carrier is expected as part of its responsibilities to make appropriate checks of patient records, examining admission, progress, and discharge notes to verify that services for which charges are billed met the appropriate coverage criteria. If the carrier review shows that a significant portion of the services in the sample do not meet the criteria, appropriate steps should be taken to adjust the reimbursement.

3. Bills must indicate when services are furnished in the teaching setting, the name of the provider and attending physician involved, and the extent of the services provided as an attending physician. The services must be defined and quantified to avoid errors in applying the reasonable charge limitation—e.g., to avoid applying the reasonable charge for a global service where only the surgical procedure or another component service was provided as an attending physician.

4. The carrier will need to carry out the steps necessary to assure itself that these conditions set out in B.1. are met—for example, to assure itself that any schedule of charges proposed for the teaching setting is actually applied and collected.

1877

D. Who may bill

Where the supervising physician is a member of a group which provides teaching services in a hospital, the Part B payment for services rendered as attending physicians by the group may be billed for:

1. by the physician or a corporation, partnership, or other organization of physicians (including an association of teaching physicians organized for the purpose of billing for and distributing insurance monies and other payments received for professional services to patients) on form 1490;

2. by the hospital on form 1554 provided that the carrier has determined that the certification described in C.1.a. has been executed and complied with; and

3. if the services are performed by a physician who is a faculty member of a medical, osteopathic, or dental school, by the school on form 1490.

The individual physician's authorization is required to be on file in writing with the hospital or other organization to permit any of the above organizations to bill on his behalf. The organization must furnish to the Part B carrier the names of the physicians who have authorized the organization to bill on their behalf, and must agree to keep the carrier informed on a current basis of changes in membership in the group.

FEBRUARY 11, 1970

WASHINGTON, D.C., *January 28, 1970.*

To: Director, Investigation and Security Service.
From: K. F. Everett, Special Investigator.
Subject: Alleged Irregularities in Payroll Practices at VAH, Nashville, Tennessee.
Period of Investigation: December 4, 1969 to December 16, 1969 and January 5, 1970 to January 9, 1970.

I. Authority

Investigation was authorized by the Deputy Administrator on November 28, 1969.

II. Matter investigated

1. During a visit of an Internal Audit Service team at VAH, Nashville on another matter, information was developed that Radiology Service was establishing and maintaining Time and Attendance records for Residents and student Technicians who are not working for VA and that this appeared to be done for the purpose of generating funds for these persons or the Medical Center at the expense of appropriated funds.

2. Bobby Moore, Management Specialist, Internal Audit Service, assisted in the investigation.

III. Narrative summary

1. Hospital records show that on July 30, 1969, a contract was entered into between the Nashville VAH and the Vanderbilt University to furnish five full-time Physicians from the Vanderbilt Department of Radiology to furnish radiology services to the VAH through June 30, 1970 at a cost of $117,300.00 per annum. The contract stipulates

61) 1969-09-03 Comptroller General of the United States: Report to the Committee on Finance United States Senate—Medicare payments for services of supervisory and teaching physicians at Cook County Hospital, Chicago, Illinois B-164031(4). National Library of Medicine, Bethesda 14, MD. W 275 AI3 U5m 1969 https://books.google.com/books?id=TVAsAAAAIAAJ&pg=PP5&lpg=PP5&dq=Medicare+Payments+for+Services+of+Supervisory+and+Teaching+Physicians+at+cook+county+hospital,+chicago,+illinois+b-164031(4)&source=bl&ots=sSRW70DaNv&sig=ACfU3U3Drb4swZ19p-w3yqjYX-pFjnegmA&hl=en&sa=X&ved=2ahUKEwjS5rOp86r0AhUDZc0KHZtaBDMQ6AF6BAgEEAM#v=onepage&q=Medicare%20Payments%20for%20Services%20of%20Supervisory%20and%20Teaching%20Physicians%20at%20cook%20county%20hospital%2C%20chicago%2C%20illinois%20b-164031(4)&f=false

Includes:
Response of Robert Freeark, M.D., Director, Associated Physicians of Cook County Hospital in a letter of July 3, 1969 to Mr. David Hanna, US GAO, pages 89-91 and Thomas Tierney, Director, Bureau of Health Insurance: Bureau of Health Insurance, Intermediary Letter No. 372.

Please see 20-2022-05-03 annotated Bibliographic Timeline References.pdf

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APPENDIX V
Page 1

COOK COUNTY HOSPITAL

GEORGE W. DUNNE, PRESIDENT
BOARD OF COUNTY COMMISSIONERS

WILLIAM H. HARVEY, COMMISSIONER
HOSPITAL CHAIRMAN

1825 WEST HARRISON STREET
CHICAGO, ILLINOIS 60612
PHONE - AREA CODE 312 - 633-6000

ROBERT J. FREEARK, M.D.
HOSPITAL DIRECTOR

FRED A. HERTWIG
SUPERINTENDENT

July 3, 1969

Mr. David Hanna
United States General Accounting Office
610 South Canal Street
Chicago, Illinois

Dear Mr. Hanna:

This will acknowledge my recent meeting with you and the opportunity it provided to review the rough draft of a proposed report by the General Accounting Offices. Other than the minor corrections which you have agreed to make, I would also ask that you make two major additions.

One of the issues which the study raises is the extent to which attending physicians are providing supervision and direction to internes and residents. While I would agree that in many instances this supervision and direction is poorly documented in the medical record, this does not mean that it was not given. In many private hospitals, the only notation in a hospital chart to indicate that a physician visited a patient or performed a procedure, is that which appears in the nurses notes. We simply do not have enough nurses to provide this documentation and it is not realistic to expect this to be done by the physicians. I believe the vast majority of "undocumented services" were so categorized because neither a doctor's or a nurse's note records a visit.

I believe Recommendations #31 and #36 of the report of the Joint Commission on Accreditation of Hospitals (February 1968) should be included in your report. These statements and the fact that our interneship and residency training programs are fully approved by the Council on Medical Education of the American Medical Association, is ample evidence that attending physicians are providing supervision and direction to our house staff. There is no doubt in my mind that patient care in a "Teaching Hospital" (one that conducts approved residency and interne training programs) is under greater scrutiny and better supervised than in hospitals without these programs.

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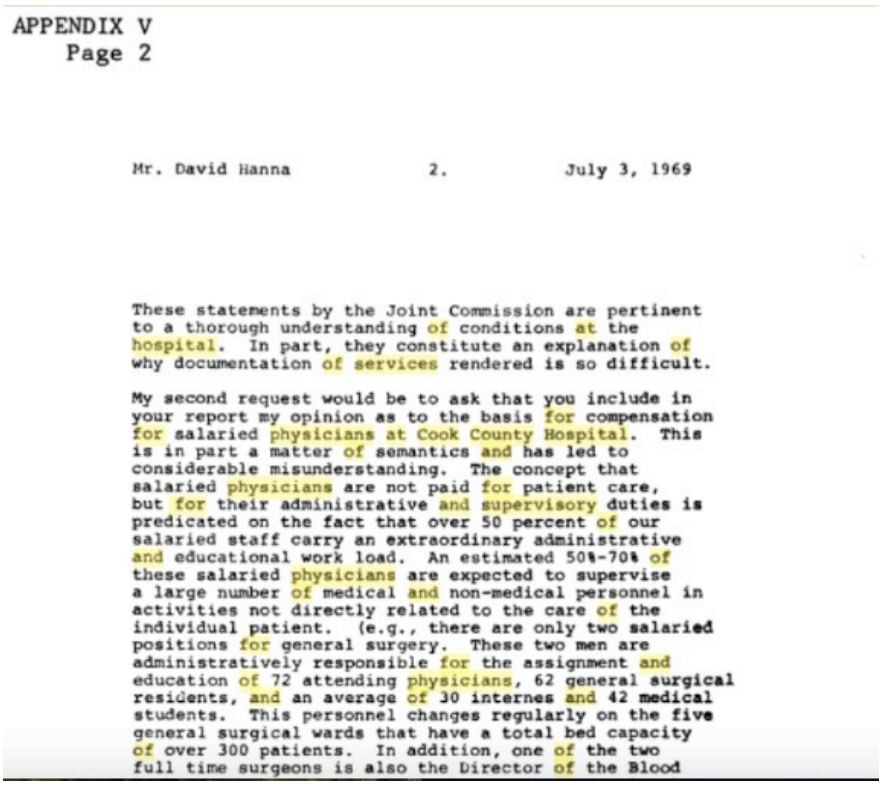
Prevention: *Active Immunization*: Vaccines



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Mr. David Hanna 2. July 3, 1969

These statements by the Joint Commission are pertinent to a thorough understanding of conditions at the hospital. In part, they constitute an explanation of why documentation of services rendered is so difficult.

My second request would be to ask that you include in your report my opinion as to the basis for compensation for salaried physicians at Cook County Hospital. This is in part a matter of semantics and has led to considerable misunderstanding. The concept that salaried physicians are not paid for patient care, but for their administrative and supervisory duties is predicated on the fact that over 50 percent of our salaried staff carry an extraordinary administrative and educational work load. An estimated 50%-70% of these salaried physicians are expected to supervise a large number of medical and non-medical personnel in activities not directly related to the care of the individual patient. (e.g., there are only two salaried positions for general surgery. These two men are administratively responsible for the assignment and education of 72 attending physicians, 62 general surgical residents, and an average of 30 internes and 42 medical students. This personnel changes regularly on the five general surgical wards that have a total bed capacity of over 300 patients. In addition, one of the two full time surgeons is also the Director of the Blood

Please see 20-2022-05-03 annotated Bibliographic Timeline References.pdf

Bank, which has 23 technical persons in its employ.)

Furthermore, at the present time, the salary paid to over 60 percent of our full time staff represents only a portion (estimate 60%-70%) of their total professional income. In addition, this salary is approximately two-thirds that paid to physicians in comparable positions in hospitals in this geographic area. Based on the extraordinary administrative and formal educational responsibilities and the concept of a partial salary for a portion of their time, I am of the opinion that when

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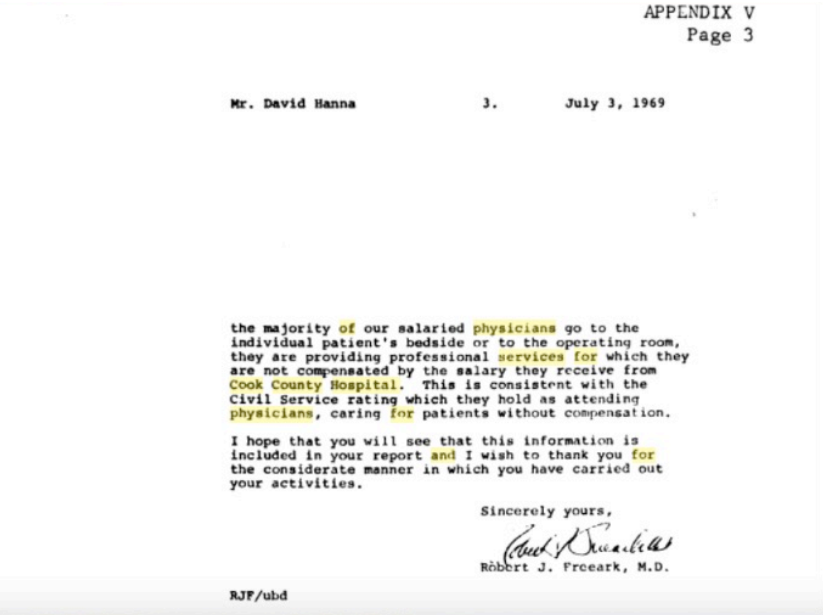

APPENDIX V
Page 3

Mr. David Hanna 3. July 3, 1969

the majority of our salaried physicians go to the individual patient's bedside or to the operating room, they are providing professional services for which they are not compensated by the salary they receive from Cook County Hospital. This is consistent with the Civil Service rating which they hold as attending physicians, caring for patients without compensation.

I hope that you will see that this information is included in your report and I wish to thank you for the considerate manner in which you have carried out your activities.

Sincerely yours,

Robert J. Freeark, M.D.

RJF/ubd

Please see 20-2022-05-03 annotated Bibliographic Timeline References.pdf

62) 1970 Anderson SG, Skegg J: The international standard for anti-smallpox serum. Bull. Wld Hlth Org 1970; 42: 515-523. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427467/pdf/bullwho00215-0018.pdf

63) 1970-02-11 Comptroller General of the United States: Regarding the GAO report of alleged overpayment to The Associated Physicians of the Cook County Hospital, B-164031(4) https://www.gao.gov/assets/b-164031%284%29-089860.pdf

64) 1973-04-28 U.S. Department of Health, Education, and Welfare, Public Health Service: FINAL REPORT of the Tuskegee Syphilis Study Ad Hoc Advisory Panel. https://biotech.law.lsu.edu/cphl/history/reports/tuskegee/complete%20report.pdf

65) 1974-06-15 Bernstein C, Woodward b: *All the President's Men*. New York: Simon & Schuster, 1974. https://en.wikipedia.org/wiki/All_the_President%27s_Men

66) 1977 Dallin A: Communism. The World Book Encyclopedia, Ci-Cz, Volume 4, Field Enterprises Educational Corporation, Chicago, 1977. P 724b-727.

> **Why Communism?** The spread of Communism is usually thought of in terms of force and revolution. However, millions of persons have freely chosen to become Communists or to vote for them.
>
> Communism has different appeals for different individuals and groups. Its main attraction for some is its claim to provide simple answers and solutions in difficult situations. Some persons join the party to avoid being outsiders, and to feel they are part of a meaningful group. Others join to ride the "wave of the future." They believe that Communist victory is inevitable.

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> The appeals of Communism seem to be strongest in countries where some of the following conditions exist. (1) There are huge differences in income and social position between the poor and rich, and the poor feel these differences. (2) Communism is the only effective movement fighting for change, reform, or revolution. (3) The existing government does not command the strong loyalty of the people, and its institutions do not stand up well under stress. (4) Many persons feel deprived and discriminated against socially and economically, and as national or racial groups. (5) Communists are not looked on as criminals or lunatics, but as one of several accepted types of revolutionaries.

67) 1978 Brandt AM: Racism and Research: The case of the Tuskegee syphilis study. The Hastings Center Report 1978; 8(6): 21-29. https://dash.harvard.edu/bitstream/handle/1/3372911/Brandt_Racism.pdf?sequence=1&isAllowed=y

68) 1979-04-01 FEMA founded. https://www.fema.gov/

69) 1979-04-18 Office of the Secretary, The National Commission for the Protection of Human Subjects of Research. The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

70) 1980 38 U.S.C. § 5705: Protection of Morbidity and Mortality conferences from legal discovery. https://www.law.cornell.edu/uscode/text/38/5705

71) 1981-04 Busuttil RW, Davidson RK, Fine J, Tompkins RK: Effect of prophylactic antibiotics in acute nonperforated Appendicitis – A prospective, randomized, double-blind clinical study. Ann Surg, Oct 1981; 194 (4): 502-509. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1345331/pdf/annsurg00212-0140.pdf

Table 9. Postoperative Infections

	Number	Per Cent
Group I (Placebo)	6/45	13.3
Group II (cefamandole preop)	1/46	2.2
Group III (cefamandole and carbenicillin preop)	0/45	0

This one study was extremely influential in the discontinuation of all placebo antibiotic studies. Subsequently all studies have been comparison studies between the new antibiotic with established antibiotics.

72) 1986-06 Hyslop JW, Maull KI: Natural history of the retained surgical sponge. South Med J 1986 Jun; 75(6): 657-660. https://pubmed.ncbi.nlm.nih.gov/7089613/

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73) 1982-06-24 U.S. Supreme Court: Nixon v. Fitzgerald, 457 U.S. 731 (1982), No. 79-1738, Argued November 30, 1981, Decided June 24, 1982.
https://supreme.justia.com/cases/federal/us/457/731/

> 2. Petitioner, as a former President of the United States, is entitled to absolute immunity from damages liability predicated on his official acts. Pp. 457 U. S. 744-758.
>
> (a) Although there is no blanket recognition of absolute immunity for all federal executive officials from liability for civil damages resulting from constitutional violations, certain officials -- such as judges and prosecutors -- because of the special nature of their responsibilities, require absolute exemption from liability. *Cf. Butz v. Economou,* 438 U. S. 478. Determination of the immunity of particular officials is guided by the Constitution, federal statutes, history, and public policy. Pp. 457 U. S. 744-748.
>
> (b) The President's absolute immunity is a functionally mandated incident of his unique office, rooted in the constitutional tradition of the separation of powers and supported by the Nation's history. Because of the singular importance of the President's duties, diversion of his energies by concern with private lawsuits would raise unique risks to the effective functioning of government. While the separation of powers doctrine does not bar every exercise of jurisdiction over the President, a court, before exercising jurisdiction, must balance the constitutional weight of the interest to be served against the dangers of intrusion on the authority and functions of the Executive Branch. The exercise of jurisdiction is not warranted in the case of merely private suits for damages based on a President's official acts. Pp. 457 U. S. 748-754.
>
> (c) The President's absolute immunity extends to all acts within the "outer perimeter" of his duties of office. Pp. 457 U. S. 755-757.
>
> (d) A rule of absolute immunity for the President does not leave the Nation without sufficient protection against his misconduct. There remains the constitutional remedy of impeachment, as well as the deterrent effects of constant scrutiny by the press and vigilant oversight by Congress. Other incentives to avoid misconduct may include a desire to
>
> Page 457 U. S. 733
>
> earn reelection, the need to maintain prestige as an element of Presidential influence, and a President's traditional concern for his historical stature. Pp. 457 U. S. 757-758.

74) 1983-05 Williams GR: Presidential Address: A history of appendicitis with anecdotes illustrating its importance. Ann Surg 1983 May; 197 (5): 495-506.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1353017/pdf/annsurg00135-0007a.pdf
(This citation is listed regarding page 504 in which the "teaching at the bedside" is epitomized by Dr. William Halsted (father of American Surgery) and Dr. William Osler (father of American Internal Medicine) weighing in on the appendicitis of Dr. Harvey Cushing (father of American Neurosurgery):

> On September 9, 1987, Dr. Harvey Cushing, then a resident in Surgery at The Johns Hopkins Hospital, operated on a patient with a ruptured appendix. The patient died ten days later of peritonitis. This experience must have increased his apprehension when, on Sunday, September 26, 1897, Cushing experienced abdominal pain and carefully recorded the development of his own episode of acute appendicitis (Fig. 14). At 9:00 am the following morning, he was seen in consultation by Drs. Halsted and Osler who did not advise operation. At 2:00 pm on the same day, he was taken to the operating room where Dr. Halstead removed his appendix. A somewhat complicated recovery followed (fig. 15).

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75) 1985-11-28 Anderson RM, May RM: Vaccination and herd immunity to infectious diseases. Nature 1985; 318: 323-329. https://www.nature.com/articles/318323a0.pdf

76) 1986-08 Condon RE: Type III Error. *Arch Surg.* 1986;121(8):877-878. doi:10.1001/archsurg.1986.01400080019002 https://jamanetwork.com/journals/jamasurgery/article-abstract/591890

> Type I and type II errors are the two classic pitfalls in statistical analysis: finding a difference when there is none (type I) and failure to find a true difference (type II). **There is, in addition, another important error that regularly appears in scientific journals. This error, *the type III error*,[1] occurs whenever the conclusions drawn are not supported by the data presented. In recent years, type III errors have been increasing in prevalence.** Some illustrations drawn from recently published articles should serve to define my point. I have deliberately omitted citation of sources because my intent is to illustrate, not embarrass.

77) 1987 Cohen SN: Chapter 37: Immunization-Passive Immunization. *Basic & Clinical Immunology*, 6.th Edition. Stites DP, Stobo JD, Wells JV (eds), Norwalk, CT/Los Altos, CA: Appleton & Lange, 1987. Pages 669-673.

78) 1987-11-12 Trump DJ with Tony Schwartz: *TRUMP The Art of the Deal.* New York: Random House, 1987. http://www.randomhousebooks.com/books/180675/

> Please note that the words "sorry" or "apologize" are not mentioned even once in this book.

79) 1990-04 Mullis KB: The unusual origin of the Polymerase Chain Reaction. A surprisingly simple method for making unlimited copies—during a moonlit drive through the mountains of California. https://cs.brown.edu/courses/csci1810/resources/pcr%20origin.pdf

80) 1992 Chard T: Review: Pregnancy tests: a review. Human reproduction 1992; 7 (5): 701-710. https://academic.oup.com/humrep/article-abstract/7/5/701/631514?redirectedFrom=fulltext

81) 1993 U.S. Institute of Medicine: *Veterans at Risk—The Health Effects of Mustard Gas and Lewisite.* Institute of Medicine (US) Committee on the Survey of the Health Effects of Mustard Gas and Lewisite. Constance M Pechura and David P Rall., eds. (Washington, D.C.: National Academies Press, 1993). https://www.ncbi.nlm.nih.gov/books/NBK236070/ and https://www.nap.edu/catalog/2058/veterans-at-risk-the-health-effects-of-mustard-gas-and

82) 1993-05 Stark A: What's the matter with business ethics? Harvard Business Review, May-June1993. https://hbr.org/1993/05/whats-the-matter-with-business-ethics

> And yet, I suspect that the field of business ethics is largely irrelevant for most managers. It's not that they are hostile to the *idea* of business ethics. Recent surveys suggest that over three-quarters of America's major corporations are actively trying to build ethics into their organizations. Managers would welcome

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> concrete assistance with primarily two kinds of ethical challenges: first, identifying ethical courses of action in difficult gray-area situations (the kind that Harvard Business School Lecturer Joseph L. Badaracco, Jr. has described as "not issues of right versus wrong," but "conflicts of right versus right"); and, second, navigating those situations where the right course is clear, but real-world competitive and institutional pressures lead even well-intentioned managers astray.

Henning PJ: When money gets in the way of corporate ethics. The New York Times, DealBook/Business & Policy, April 17, 2017. https://www.nytimes.com/2017/04/17/business/dealbook/when-money-gets-in-the-way-of-corporate-ethics.html

83) 1993-06-03 Dingell JD: Shattuck Lecture – Misconduct in Medical Research. N Engl J Med 1993 June 3; 328(22): 1610 – 1615. https://www.nejm.org/doi/pdf/10.1056/NEJM199306033282207?articleTools=true

84) 1993-07 Allen JB: Possessed. https://archive.org/details/possessedtruesto00alle/page/n5/mode/2up

85) 1995 Casadevall A, Scharff MD: Return to the past: the case for antibody-based therapies in infectious disease. Clin Infect Dis 1995; 21(1): 150-161. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197598/pdf/21-1-150.pdf

86) 1995 Mudd R: Last secrets of the Axis. https://www.youtube.com/watch?v=d5ARbOVpFqc

87) 1995-01-04: Meyer HS: *Gordon's Guide to the Surgical Morbidity and Mortality Conference.* JAMA 1995; 273(1): 86-87. https://jamanetwork.com/journals/jama/article-abstract/385539

> Gordon advocates inclusiveness and honesty about complications—"An untoward event contributing to morbidity or mortality is a complication whether it is expected, anticipated, or not," and no type is exempt from presentation. He asserts that the familiarity a trainee gains at the M and M meeting with complications and their management is crucial to professional surgical development. He wishes training programs would resurrect the surgical notebook and the complications notebook, and the departments would devote real resources to M and M, including hiring an M and M secretary. …

88) 1995-11 Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration: Guidance for Industry, Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Charaterized, Therapeutic, Biotechnology-derived Products. https://www.fda.gov/media/72057/download

89) 1996 Internet Archive: About the Internet Archive—a 501 (c)(3) non-profit building a digital library of Internet sites and other cultural artifacts in digital form. 300 Funston Ave,

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Prevention: *Active Immunization*: Vaccines

San Francisco, CA 94118 https://archive.org/ (Throughout this bibliography, the Wayback Machine of the Internet Archive has been used to identify earlier overwritten documents within the same URL.). https://archive.org/web/

90) 1996 Thall PF, Simon RM, Estey EH: New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.989.470&rep=rep1&type=pdf

91) 1996-08-30 Fauci AS: Letter to C.Everett Koop on his 80th birthday. https://profiles.nlm.nih.gov/spotlight/qq/catalog/nlm:nlmuid-101584930X417-doc

…When people heard that I was a close friend of yours, they often asked me what it was like to know you and how impressed they were that you were a very unpredictable individual. I responded very confidently that, in fact contrary to their impressions, you were one of most predictable individuals that I had ever met. All one had to do was be insightful enough to figure out what the correct approach would be under unusually trying circumstances. Once you have that figured out, then Chick Koop is the most predictable person in the world because he always seems to do what is the most correct, honorable, and appropriate thing for the health of the Nation. This is your legacy and it is something for which you should be truly proud.

92) 1997 Shuster E: Fifty years later: The significance of the Nuremberg Code. N Engl J Med 1997; 337 (20): 1436-1440. https://www.nejm.org/doi/pdf/10.1056/NEJM199711133372006?articleTools=true

93) 1997 Raffensburger J: Cook County Hospital. Encyclopedia of Chicago Cook County Hospital; *The Old Lady on Harrison Street: Cook County Hospital, 1833-1995.* Raffensburger JG, Boshes, eds. *International Healthcare Ethics, vol 3, 1997.* http://www.encyclopedia.chicagohistory.org/pages/336.html

94) 1997 Fisher JT: Dr. America. The Lives of Thomas A. Dooley 1927 - 1961. Amherst: University of Massachusetts Press, 1997. While Thomas Dooley, M.D. will always be a controversial, self-proclaimed, self-promoting figure in American history, his founding of his more than 20 clinics (MEDICO) in Southeast Asia after the conclusion of the French Indochina war was acclaimed at the time and their concept would be foundational in the establishment of Medecins Sans Frontieres (Doctors without borders). https://muse.jhu.edu/article/4109

95) 1997 Foley, John S.J. Peace Prayer. https://songstranslation.com/john-foley/peace-prayer/ https://www.youtube.com/watch?v=4vVlCXJt0Y4

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Lyrics: Beautiful adaptation of the Prayer of Saint Francis of Assisi Peace Prayer --
Music and Lyric John Foley, SJ

1… Lord make me a means of Your Peace
Where there's hatred grown
Let me sow Your love
Where there's injury Lord
Let forgiveness be my sword
Lord make me a means of Your Peace
2… Lord make me a means of Your Peace
When there's sadness here
Let me sow Your joy
When the darkness nears
May Your light dispel our fears
Lord make me a means of Your Peace
3… Lord grant me to seek and to share
Less to be consoled
Than to help console
Less be understood
Than to understand Your good
Lord make me a means of Your Peace
4… Lord grant me to seek and to share
To forgive in thee
You've forgiven me
For to die in thee
Is eternal life to me
Lord make me a means of Your Peace

96) 1997-05-16 Clinton WJ: Remarks by the President in apology for study done in Tuskegee. THE WHITE HOUSE, Office of the Press Secretary. https://clintonwhitehouse4.archives.gov/New/Remarks/Fri/19970516-898.html

97) 1997-10-21 Cohen JJ: Statement of the AAMC on DHHS Inspector General "PATH" audits presented to the Subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Committee on Appropriations, United States Senate. https://www.aamc.org/media/15286/download?attachment

98) 1997-10-21 Cohen JJ: Statement of the Association of American Medical Colleges on DHHS Inspector General "Path" Audits presented to the subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Committee on Appropriations, United States Senate. https://www.aamc.org/media/15286/download?attachment This very important AAMC response is regards to the PATH audits based on compliance with IL-372.

99) 1997-12 Feinstein AR, Horwitz RI: Problems in the "Evidence" of "Evidence-based medicine." Am J Med 1997 Dec; 103 (6): 529-535. https://www.sciencedirect.com/science/article/abs/pii/S0002934397002441

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Abstract

The proposed practice of "evidence-based medicine," which calls for careful clinical judgment in evaluating the "best available evidence," should be differentiated from the special collection of data regarded as suitable evidence. Although the proposed practice does not seem new, the new collection of "best available" information has major constraints for the care of individual patients.

Derived almost exclusively from randomized trials and meta-analyses, the data do not include many types of treatments or patients seen in clinical practice; and the results show comparative efficacy of treatment for an "average" randomized patient, not for pertinent subgroups formed by such cogent clinical features as severity of symptoms, illness, co-morbidity, and other clinical nuances. The intention-to-treat analyses do not reflect important post-randomization events leading to altered treatment; and the results seldom provide suitable background data when therapy is given prophylactically rather than remedially, or when therapeutic advantages are equivocal. Randomized trial information is also seldom available for issues in etiology, diagnosis, and prognosis, and for clinical decisions that depend on pathophysiologic changes, psychosocial factors and support, personal preferences of patients, and strategies for giving comfort and reassurance.

The laudable goal of making clinical decisions based on evidence can be impaired by the restricted quality and scope of what is collected as "best available evidence." The authoritative aura given to the collection, however, may lead to major abuses that produce inappropriate guidelines or doctrinaire dogmas for clinical practice.

100) 1998-07 United States General Accounting Office: Report to the Chairman, Subcommittee of Health, Committee on Ways and Means, House of Representatives: MEDICARE—concerns with Physicians at Teaching Hospitals (PATH) Audits, GAO/HEHS 98-174 https://www.gao.gov/assets/hehs-98-174.pdf

101) 1998-08-12 36 U.S. Code 302 – National motto: "In God we trust" is the national motto. PL-105-225, Aug. 12, 1998, 112 Stat. 1263; PL 107-293, 3(a), Nov 13, 2002, 116 Stat 2060. https://www.law.cornell.edu/uscode/text/36/302

102) 1999-11-22 Office of Inspector General, U.S. Department of Veterans: Combined Assessment Program review: Edward Hines, Jr. VA Hospital, Hines, IL. Report No.99-00173-18, Date: November 22, 1999. Appendix IV, pages 43-61 are documentation of my oversight responsibilities as Chief of Surgery, Edward Hines, Jr. VAH 1996 – 2002. [which VACO cannot misplace as they have my Official Professional File (OPF) of between April 1982 through August 2016] https://www.va.gov/oig/cap/99-00173-18.pdf **Please note that on pages 43-44 is: October 14, 1999….Charles H. Andrus, M.D., F.A.C.S., Chief, Surgical Service**—the Office of Inspector General in Report No. 99-00173-18 of November 22, 1999 failed to do what is stated on the face page of the document: **FULLY-REDACTED ELECTRONIC COPY FOR PUBLIC RELEASE**

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

103) 1999-12-10 Andrus CH: Interviewed by the U.S. Department of Veterans Affairs, Veterans Health Administration 1999 Under Secretary for Health Commission for the position of Under Secretary for Health, Veterans Health Administration.

104) 2000 Institute of Medicine (US) Committee on Quality of Health Care in America; Kohn LT, Corrigan JM, Donaldson MS, editors. To Err is Human: Building a Safer Health System. Washington (DC): National Academies Press (US); 2000. https://www.ncbi.nlm.nih.gov/books/NBK225182/

105) 2000-01 Kirkeby L, Rasmussen TT, Reinholdt J, Kilian M: Immunoglobulins in nasal secretions of healthy humans: Structural integrity of secretory immunoglobulin A1 (IgA1) and occurrence of neutralizing antibodies to IgA1 proteases of nasal bacteria. Clin Diagn Lab Immunol 2000; 7: 31-39 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC95818/pdf/cd000031.pdf

106) 2000-01 Axelrod DA, Dorr Goold S: Maintaining trust in the surgeon-patient relationship: *Challenges for the New Millenium*. Arch Surg 2000; 135 (1) : 55 – 61. https://jamanetwork.com/journals/jamasurgery/fullarticle/390488

107) 2001-02 Auerbach AD, Davis RB, Phillips RS: Physician views on caring for hospitalized patients and the hospitalist model of inpatient care. JGIM 2011 Feb; 16 : 116 - 119 . https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1495177/pdf/jgi_91154.pdf

108) 2001-03 La Vaque TJ, Rossiter T: The ethical use of placebo controls in clinical research: Appl Psychophysiol Biofeedback 2001; 26 (1): 23 – 37. https://link.springer.com/article/10.1023/A:1009563504319

109) 2001-03-31 Hoots WK, Abrams C, Tankersley D: The Food and Drug Administration's perspective on plasma safety. https://pubmed.ncbi.nlm.nih.gov/11441417/

110) 2001-04-01 Andrus CH, Johnson K, Pierce E, Romito PJ, Hartel P, Berrios-Guccione S, Best W: Finance modeling in the delivery of medical care in tertiary-care hospitals in the Department of Veterans Affairs. J Surgical Research.2001 Apr 01; 96 (2): 152 – 157. https://www.journalofsurgicalresearch.com/article/S0022-4804(99)95728-1/pdf

111) 2001-05 U.S. Department of Health and Human Services, Food and Drug Administration, , Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER): Guidance for Industry—E 10 Choice of Control Group and Related Issues in Clinical Trials. May 2001. https://www.fda.gov/media/71349/download (E10 Choice of control group and related issues in clinical trials, content current as of 8/24/2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e10-choice-control-group-and-related-issues-clinical-trials)

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112) 2001-05-15 VA Office of Public and Intergovernmental Affairs: Under Secretary for Health announces intent to resign. https://www.va.gov/opa/pressrel/pressrelease.cfm?id=269

113) 2001-06 Meltzer D: Hospitalists and the doctor-patient relationship. J Legal Stud 2001 Jun; 30 (2): 589 – 606. https://pubmed.ncbi.nlm.nih.gov/12647747/ for abstract and for full paper: https://www.jstor.org/stable/10.1086/339294

114) 2001-07-01 Richelson JT: When Secrets Crash. Air Force Magazine. https://www.airforcemag.com/article/0701crash/

> On Sept. 24, 1959, Thomas L. Crull was flying a newly arrived U-2C, Article 360, on a local flight, heading back to Atsugi after setting an altitude record. As the U-2's fuel ran low, the airplane suffered a flameout–forcing Crull to make a dead-stick, wheels-up landing at the Fujisawa glider strip, 10 miles from Atsugi. Crull emerged unhurt, but his airplane overran the runway and slid onto the grass.
>
> Letting the airplane simply sit there unguarded was not an option. A short time later several security personnel, apparently wearing loud Hawaiian shirts and packing large revolvers, showed up and began to order the growing crowd at gunpoint to stand away from the secret aircraft. The tactic proved counterproductive as it only led to extensive publicity about the crash landing. Eventually, the airplane would be packed off to the US, repaired, and returned to service with Det. B in Turkey.
>
> From there, that airplane would make its final flight. It came on May 1, 1960, and its pilot was Francis Gary Powers. Powers was flying high over Sverdlovsk, USSR, when his U-2 came under attack by some 14 surface-to-air missiles. The U-2 broke apart, but Powers parachuted down safely and was captured, given a trial, and sentenced to 10 years in a labor camp. He was freed in 1962 in an exchange for the Soviet spy, Rudolf Abel.

115) 2001-09-20 Emanuel EJ, Miller FG: The ethics of placebo-controlled trials – A middle ground. N Engl J Med 2001; 345: 915-919. https://www.nejm.org/doi/pdf/10.1056/NEJM200109203451211?articleTools=true

116) 2001-10-25 Garthwaite TL: Resident Supervision. VHA Handbook 1400.1, U.S. Department of Veterans Affairs, Veterans Health Administration, Transmittal Sheet, October 25, 2001 and **5. Rescissions:** This VHA Handbook rescinds VHA Handbook 1400.1, March 21, 2000.

> https://www.va.gov/oaa/1400_1hk_Oct2001.doc returns the VA official website which states: **Sorry – we can't find that page**. Using the Wayback Machine, for 2004-10-28: http://web.archive.org/web/20041028182959/https://www.va.gov/oaa/1400_1hk_Oct2001.doc which states on pages 8 – 9:
>
> > **(3) Level 3.** The staff practitioner is immediately available in the facility – campus for direct resident supervision according to local policy as approved by the Network Academic Affiliations Officer. The service chief is responsible for periodically reviewing cases done under Level 3 supervision to ensure that such supervision is appropriate.

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Using the Wayback Machine another version of the Level 3 Supervision (now Level D) is identified: In VHA Handbook of July 27, 2005 signed by Jonathan B. Perlin, M.D. https://web.archive.org/web/20051107072236/http:/www.va.gov:80/OAA/1400_1hk_July27_05.doc (Recission of the previous version of May 3, 2004 which cannot be found):

> 4. **Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and immediately available for resident supervision or consultation as needed.

Using the only other "hit" on the Wayback Machine of December 21, 2016, http://web.archive.org/web/20161221045318/http://www.va.gov/oaa/1400_1hk_Oct2001.doc VHA 1400.1 has been removed completely and in its place is the website of the U.S. Department of Veterans Affairs which states: "Page Not Found." ***De facto*, the U.S. DVA, VHA misdirected official government documentation which is tantamount to destruction of evidence used in the trial of Andrus v VA, U.S. Court of Appeals for the Federal Circuit, docket # 03-3162.**

117) 2001-11-17 FBI: History: Amerithrax or Anthrax Investigation. https://www.fbi.gov/history/famous-cases/amerithrax-or-anthrax-investigation

118) 2002 Kennedy C: *Profiles in Courage for our time*. Woodward, Bob: Gerald R. Ford. New York: Hyperion, 2002. Pages 293-318. https://www.jfklibrary.org/about-us/news-and-press/press-releases/profiles-in-courage-for-our-time

> Each of these men displayed a rare form of courage, sacrificing their own future, and that of their families, to do what they believed was right for the country. Their example comes down to us across the years, their stories are part of our history, and their spirt lives on. The John F. Kennedy Profile in Courage Award is presented annually to an elected official who carries on this tradition. When we created the award in 1990, some doubted we would be able to find politicians worthy of the honor. They were wrong. This book tells the stories of men and women at all levels of government, in all parts of our country, across the political spectrum, who have all stood fast for the ideals of America.

119) 2002 Eye witness to history: "Julius Caesar Crosses the Rubicon, 49 BC," EyeWitness to History. http://www.eyewitnesstohistory.com/caesar.htm

120) 2002 Proteintech Group: (Copyright 2002-2022) Polyclonal vs. monoclonal antibodies. Proteintech https://www.ptglab.com/news/blog/polyclonal-vs-monoclonal-antibodies/

121) 2002-04-25 Breman JG, Henderson DA: Diagnosis and management of smallpox. N Engl J Med, April 25, 2002; 346 (17): 1300-1308. https://www.nejm.org/doi/pdf/10.1056/NEJMra020025?articleTools=true

122) 2002-08-28 Watts J: Japan guilty of germ warfare against thousands of Chinese—Tokyo judges rule that second world war atrocities did take place but reject claims for compensation. The Guardian For200years https://www.theguardian.com/world/2002/aug/28/artsandhumanities.japan

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

123) 2003-01-03 FDA, Center for Biologics Evaluation and Research (CBER): Guidance for Industry—Recommendations for deferral of donors and quarantine and retrieval of blood and blood products in recent recipients of smallpox vaccine (Vaccinia Virus) and certain contacts of smallpox vaccine recipients. https://www.federalregister.gov/documents/2003/01/03/03-113/guidance-for-industry-recommendations-for-deferral-of-donors-and-quarantine-and-retrieval-of-blood

124) 2003 Wei A, Juneja S: Bone marrow immunohistology of plasma cell neoplasms. J Clin Pathol 2003; 56: 406-411. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1769975/pdf/jcp05600406.pdf

125) 2003 Yu WC, Hui DSC, Chan-Yeung M: Antiviral agents and corticosteroids in the treatment of severe acute respiratory syndrome (SARS). (Editorials in the British Medical Journal). www.thoraxjnl.com , https://thorax.bmj.com/content/thoraxjnl/59/8/643.full.pdf

126) 2003-01-16 Gawande AA; Studdert DM, Orav EJ, Brennan TA, Zinner MJ: Risk factors for retained instruments and sponges after surgery. N Engl J Med 2003 Jan 16; 348(3): 229-235. https://www.nejm.org/doi/pdf/10.1056/NEJMsa021721?articleTools=true

127) 2003-03-03 Andrus CH: Andrus v VA. U.S. Court of Appeals, Federal Circuit. Case 03-3162. Oral arguments, March 3, 2004. The U.S. Court of Appeals, Federal Circuit's ruling in the case of Andrus v. VA was to fail to rule, *per curiam.* https://dockets.justia.com/docket/circuit-courts/cafc/03-3162

> Andrus CH: To Care for Him Who Shall Have Borne the Battle, And for his Widow, and his Orphan—*A. Lincoln*. Registered in the Copyright Office of the U.S. Library of Congress, USA, April 5, 2004, ©TXu1-173-542, (Revised with cover letter, table of contents, and correspondence with the Office of the Counsel to the President: August 24, 2004, ©TXu1-196-220). A compilation of documents related to U.S. Court of Appeals for the Federal Circuit Case 03-3162 *Andrus v. VA*, VA OIG Inspector General Reports regarding VHA Part-Time Physician Time and Attendance and alleged inappropriate transfers of VA patients, and correspondence with the Office of the Counsel to the President. [Was submitted and has been included in the unpublished BioEthics collection of the Joseph and Rose Kennedy Institute of Ethics, Georgetown University, National Reference Center for Bioethics Literature supported by the U.S. National Library of Medicine. Notified on Sept. 13, 2004 that the title and table of contents of this manuscript are to be added to the library's "ETHX on the Web" at http://bioethics.georgetown.edu in September/October, 2004]

128) 2003-03-28 CDC—MMWR: Cardiac adverse events following smallpox vaccination – United States, 2003. Morbidity and Mortality Weekly Report, March 28, 2003; 52 (12); 248-250. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a2.htm Subsequent MMWR July 11, 2003: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5227a4.htm Subsequent MMWR August 29, 2003: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5234a4.htm

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129) 2003-04-23 U.S. Department of Veterans Affairs, VA Office of Inspector General: Audit of the Veterans Health Administration's Part-time Physician Time and Attendance. Report no. 02-01339-85, April 23, 2003. https://www.va.gov/oig/52/reports/2003/VAOIG-02-01339-85.pdf

130) 2003-05-08 Griffin RJ: Statement of the Honorable Richard J. Griffin, Inspector General, Department of Veterans Affairs Hearing on Past and Present Efforts to Identify and Eliminate Fraud, Waste, Abuse, and Mismanagement in Programs Administered by the Department of Veterans Affairs before the Committee on Veterans Affairs www.va.gov/OCA/testimony/hvac/03my08IG.asp

131) 2003-05-07 Andrus CH, Kleinman BS, Mozdzierz GJ, Sinacore JM, Garthwaite TL: Mortality outcomes and attending surgeon presence at the time of operation. Presentation before the Association for Surgical Education (ASE). https://web.archive.org/web/20040414163722/http://www.surgicaleducation.com/pdf/mortoutcomesattending.pdf

From slide 10:

The coefficient of determination (r^2) was 0.77 which indicates 77% of the variance of O/E ratios was attributable to the % of Attending Surgeons presence (and 23% was not)

On the next day, May 8, 2003, Richard Griffin, Inspector General, U.S. Department of Veterans Affairs testified before the Veterans Affairs Committee of the U.S. House of Representatives regarding "efforts to identify and eliminate fraud, waste, abuse, and mismanagement in programs administered by the Department of Veterans Affairs." His testimony was a summary of a previous month's report from the Office of Inspector General entitled: *Audit of Veterans Health Administration's part-time physician time and attendance*. The audit which was discussed in the previous reference. https://www.va.gov/oig/pubs/statements/VAOIG-Testimony_5-8-03_US_House_of_Representatives_Cmte_on_Veterans_Affairs.pdf

132) 2003-05-12 Huang Y: The SARS epidemic and its aftermath in China: A political Perspective. Institute of Medicine (US) Forum on Microbial Threats; Knobler S, Mahmoud A, Lemon S, *et al*, editors. Washington (DC): National Academies Press (US); 2004. https://www.ncbi.nlm.nih.gov/books/NBK92479/

This paper is adapted from the Politics of China's SARS Crisis. *Harvard Asia Quarterly* (Autumn 2003). An earlier version of the article appeared in "Dangerous Secrets: SARS and China's Healthcare System," Roundtable before the Congression-Executive Commission on China, May 12, 2003, www.cecc.gov

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133) 2003-05-12 Takada A, Kawaoka: Antibody-dependent enhancement of viral infection: molecular mechanisms and *in vivo* implications. Rev Med Virol 2003; 13: 387-398. https://onlinelibrary.wiley.com/doi/full/10.1111/vox.12386

134) 2003-06-01 Andrus CH, Villasenor EG, Kettelle JB, Roth R, Sweeney AM, Matolo NM: "To err is human": Uniformly reporting medical errors and near misses, a naïve, costly, and misdirected goal. J Am Col Surg 2003 June 1; 196 (6): 911-918. https://pubmed.ncbi.nlm.nih.gov/12788428/

> Andrus CH, Villasenor EG, Kettelle JB, Roth R, Sweeney AM, Matolo NM: "To Err is Human": Uniformly Reporting Medical Errors and Near Misses: A Naïve, Costly and Misdirected Goal. J Am Coll Surg 196(6): 911-918, June 2003. [Was requested on January 29, 2004 by Doris Goldstein, M.L.S., M.A., Director, National Reference Center for Bioethics Literature for inclusion in the collection of published bioethical articles of the Joseph and Rose Kennedy Institute of Ethics, Georgetown University, National Reference Center for Bioethics Literature supported by the U.S. National Library of Medicine. Added to the library's "ETHX on the Web" at http://bioethics.georgetown.edu in August, 2004.]

135) 2003-08 Orlander JD, Fincke BG: Morbidity and Mortality Conference—A Survey of Academic Internal Medicine Departments. J Gen Intern Med 2003; 18(8): 656-658. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1494908/pdf/jgi_20824.pdf

136) 2003-11-10 Andrus CH: Ethical issues in "medicine" that touched our family. U.S. Copyright Office, TXu001145557 https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=2&ti=1,2&Search%5FArg=Andrus%20Charles%20H&Search%5FCode=NALL&CNT=25&PID=711zUFrXvEu8UUeMe4Encu1iAYnRa&SEQ=20220305181742&SID=2

137) 2004-01-11 Barry JM: The site of origin of the 1918 influenza pandemic and its public health implications. Journal of Translational Medicine – BioMed Central. www.ncbi.nlm.nih.gov/pmc/articles/PMC340389/pdf/1479-5876-2-3.pdf

138) 2004-03-03 Andrus CH: *Andrus v VA*: Oral arguments regarding Resident Supervision in the OR before a three judge panel of the U.S. Court of Appeals for the Federal Circuit. Oral arguments, March 3, 2004. The U.S. Court of Appeals, Federal Circuit's ruling in the case of Andrus v. VA was to fail to rule, *per curiam*. https://dockets.justia.com/docket/circuit-courts/cafc/03-3162

139) 2004-03-16 Andrus CH: Correspondence from the US Office of Special Counsel in Andrus v. VA and allegations of obstruction of justice / compiled by Charles H. Andrus. U.S. Copyright Office, TXu001165703. https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=11&ti=1,11&Search%5FArg=Andrus%20charles%20h&Search%5FCode=NALL&CNT=25&PID=y78dIAKyanVeyTb6Zs2tE9R4etD9sLF&SEQ=20210515161739&SID=5

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140) 2004-04-05 Andrus CH: To care for him who shall have borne the battle and for his widow and his orphan. U.S. Copyright Office, TXu001173542. https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=12&ti=1,12&Search%5FArg=Andrus%20charles%20h&Search%5FCode=NALL&CNT=25&PID=XsOYHcY7XWAupNoXfDBOnuAs5Sn75IS&SEQ=20210515162652&SID=9

141) 2004-04-14 Guo JP, Petric M, Campbell W, McGeer PL: SARS corona virus peptides recognized by antibodies in the sera of convalescent cases. Virology 2004; 324: 251-256. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7125913/pdf/main.pdf

142) 2004-04-05: U.S. Department of Veterans Affair, Office of Public and Intergovernmental Affairs: VA Under Secretary for Health Resigns. https://www.va.gov/opa/pressrel/pressrelease.cfm?id=742

143) 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212).

After OIG Inspector Griffin's testimony on May 8, 2003, ABC *Primetime* investigated for an entire year and on April 8, 2004, aired Fighting for Care narrated by Diane Sawyer. 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212) This episode was removed from the ABC Archives possibly because ABC to hidden cameras into the Cleveland and Waco VAMCs. 2004 George Polk Award for "**Television Reporting: Diane Sawyer** and **Robbie Gordon**, ***ABC News PrimeTime Live***, for **"Fighting for Care,"** which documented patient abuse and deplorable conditions in VA hospitals." (for investigative reporting excellence) https://liu.edu/polk-awards/past-winners#2004. When Tammy Shehari, the Associate Producer for the episode, spoke with me by phone in 3/2004, she asked me to estimate how many additional veterans had died due to unsupervised operations performed by Surgery Residents– I declined to guess because to do so would be wrong and a disservice to the Veteran patients and the men and women of Department of Veterans Affairs that do their duty faithfully for Veteran patients. (The interview ended shortly after my refusing to guess, and this was the only time ABC News spoke with me.)

Please note the reference above -- VHA USH, Robert Roswell, M.D. resigned three days prior to the airing of *Fighting for Care*. *Fighting for Care* contained within unauthorized hidden cameras in the Cleveland VAMC and the Waco VAMC. The VA spin was: …Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. …. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

https://web.archive.org/web/20040409151345/http://abcnews.go.com/sections/Primetime/Living/VA_Hospitals_040408-1.html

(Somewhere between Sept 1, 2004 and October 9, 2004, Fighting for Care was take off ABC News' Website when one uses the internet archive.—Charles Andrus, M.D., 3-20-2022)
Recently, there have been new stories of misdiagnosis, disastrous management and deficient care at some of the nation's 162 facilities.

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At a hospital near Cleveland, an ABCNEWS hidden-camera investigation found bathrooms filthy with what appeared to be human excrement. Supply cabinets were in disarray, with dirty linens from some patients mixed in with clean supplies, or left in hallways on gurneys.
At a neighboring facility, examining tables had dried blood and medications still on them. In several areas, open bio-hazardous waste cans were spilling over. *Primetime* obtained internal memos documenting that the equipment used to sterilize surgical instruments had broken down — causing surgical delays and possible infection risks.
With 130,000 young American men and women putting their lives at risk in Iraq today, these conditions are particularly relevant. While current soldiers are treated in military hospitals, when they leave the service and need treatment, many will seek care at Veterans Affairs (as the Veterans Administration is now known) hospitals.
"Once you come back to be a veteran, it's like a black hole, you know — nothing," former Army Sgt. Vannessa Turner told ABCNEWS.
Turner was stricken with a mysterious illness while on duty in Iraq this past year. She retired from the military on medical grounds, and when she reported to a VA hospital for treatment, doctors scheduled her for an appointment six months later.

Not a Point of Pride

Veterans who responded to a survey by the American Legion in 2003 said it took an average of seven months to get a first appointment at a VA hospital. In some hospitals, patients have waited as long as two years.
In 1999, Jack Christensen, a former army sergeant who served in the Korean War, was admitted to the VA hospital in Temple, Texas, with pneumonia, and ended up staying three years.
Christensen's wife, Pat, says the attitude of some of the practical nurses was shocking. Some of the patients were forced to beg for food and water, she says. Instead of helping her husband go to the bathroom, she said, "they would put a towel under his hips and tell him to use the towel."
Pat Christensen said her husband's condition worsened over several months — so badly that at one point he developed horrific bedsores and dangerous infections, and she says his doctors said they would have to amputate his legs.
Pat moved her husband to a private facility, where his infection healed and he underwent extensive physical therapy. She sued the VA, and then used the money to pay for private care for her husband. The VA denied liability but paid a settlement.
Dr. Jonathan Perlin, the deputy undersecretary for health, said the VA system has sophisticated quality control. But when he was shown ABCNEWS' hidden-camera video of hallways and supply closets in disarray, he said, "This is something we're not proud of."

Fundamental Problems

Critics have long charged that the VA system puts patients on a kind of assembly line, passing them from doctor to doctor.
There's also criticism of how the VA uses residents — doctors still training and not certified in their specialties. Terry Soles served in the Navy during the Vietnam War. His wife, Denise, says he was one casualty of this practice. In 1998, he went to the VA hospital in Cleveland complaining of pain and diarrhea, and doctors removed small cancerous growths from his stomach and esophagus.
But as his symptoms persisted over the next two years, his wife says the VA gave him painful tests and repeatedly lost the results. His wife says Soles was seen by a parade of constantly rotating resident doctors, and there was little consistency in his care.
Once, Soles was prepped for surgery but before the operation the doctors who were present couldn't agree on what they were going to do, she said.
Before he got sick, the 6-foot Soles weighed more than 200 pounds. By the time his family finally decided to take him to a private hospital, he weighed 80 pounds. Some VA doctors thought his problem was psychosomatic.
When he could no longer recognize his own son, Soles was rushed to a private hospital. There, Soles learned he was "a total mass of cancer from his trachea to his renal bowel. And that there was nothing that could be done," his wife says. Terry Soles died three days later.
The VA's Perlin said the Soles story was tragic, but added: "However, that is not the experience of most of the veterans who come to us for care. … We take care of 7 million veterans. While the majority of care is good, in a big system, bad things happen."

Whose Fault?

Critics charge that one of the big problems facing the VA is that too much money goes toward administration, at the cost of nursing and patient care.
Dean Billik, the former director of the VA in Charleston, S.C., is brought up as an example.
In 1996, he was denounced for allegedly spending about $200,000 in taxpayer money to redecorate his office; $1.5 million to renovate a nursing home unit that stayed empty for two years; and tens of thousands of dollars for a fish tank in the lobby — while there were budget shortfalls and staff cutbacks were contemplated.
Congress heard testimony claiming Billik was "blatant in his mismanagement," and an inspector general's report confirmed several of the numerous allegations against him.
But after everything was brought to light, Billik still got a bigger job: He was put in charge of the third-largest hospital system in the VA, encompassing eight cities, 295 acres of land and 83 buildings. And his salary immediately jumped about $15,000.

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Primetime obtained budget information on the central Texas VA system for Billik's six-year tenure at the top. It confirms that Billik cut spending $2 million for the people in direct patient care — nurses aides and practical nurses.
Other documents obtained by *Primetime* show that $129 million was spent on construction at three of six facilities in Temple, Texas.
One source says Billik spent $1.8 million renovating a building at Temple for his own offices — after it had been renovated for patient care.
Furthermore, Nancy Kelsey, who was a nurse at one of the Temple facilities under Billik's supervision, says the way some of the staff treated patients was alarming. She says IVs ran out, patients were neglected and dressings weren't changed.
Melba Bell, whose husband, Ed, served in Korea, said the staff was often idle and it would often take hours to get help. Other families said that if patients or their families persisted in asking for help, some of the staff retaliated.
At one point, Bell's infection got so bad that the hospital used maggots to try to eat away the decay. That's not unusual treatment, but what happened afterward was.
"The dressing that they had on there was real poorly done," said Bell's granddaughter, Chesney Shirmer. "Some of the maggots got out and they were in the bed with him, you know? He could feel them in the bed."
Ed Bell died of gangrene in the VA hospital in 2002.

One More Problem

When confronted with these details, Perlin said he shared the outrage and promised to look into fixing these things.
But there is one more problem. Many whistle-blowers and critics say if you try to expose the truth, VA managers don't want to hear it.
Charles Steinert, who worked for Billik in Charleston, says he felt pressure to leave after he complained about some of the building projects and how he was being treated by supervisors.
Nurse Melissa Craven, who also worked at the Charleston VA, says she suffered retribution for two years after she spoke out about some of her supervisors.
Perlin said it is easy for patients and their loved ones to lodge complaints about VA care. "That's important to us, because if there are concerns, we want to address them," he said.
But many patients and their loved ones told ABCNEWS that wasn't their experience — and even worse, many of the families are afraid to speak out.
"They're afraid to say what really goes on, because they're afraid any little benefits that they have are going to be taken away from them," said Denise Soles.

Improvement Efforts

The day after *Primetime* presented its findings to the VA's Perlin, he ordered inspections of the facilities *Primetime* investigated.
They found a number of problems at the Temple, Texas, VA, including poor hygiene, insufficient staffing and low satisfaction among patients and their families.
The VA announced it would bring in new supervisors, reassign some personnel, train others, and begin recruiting additional staff.
Inspectors who went to the VA in Cleveland said it was in good condition. However, after their visit, *Primetime* received phone calls from several sources saying that the hospital had advance warning of the so-called surprise inspection.
And to those patients who accuse the VA of assembly-line care — that patients go through a succession of doctors — a public relations officer for the VA said it tries to ensure continuity of care, but that may not always be possible.
As for Dean Billik, he has now retired. In a phone conversation on Wednesday, he said he disagreed with the VA inspectors, saying their report was "an opinion."
Billik said he relied on his staff to supervise nursing and recommend budgets, and if he had renovated some buildings that then were closed it was because he didn't possess 20/20 hindsight and made the best decisions at the time.
Rep. Ted Strickland, a member of the House Veterans Affairs Committee, called for the White House and Congress to approve enough money to ensure that veterans get the care they deserve.
It's a "situation that's crying out for change," the Ohio Democrat said after viewing *Primetime's* tapes.
Veterans and their families agree they deserve better. "They were good enough to go fight for their country," said Melba Bell. "They deserve to have the best treatment that they could get."
Denise Soles says that before her husband died he asked just one thing of her: to speak out.
She said Terry Soles told her, "If we can help one other veteran from going through the hell … That's what we have to do." ■

Some Internet resources for veterans: **GIreports**, http://www.gireports.com; **Iraq War Veterans Organization**, http://www.iraqwarveterans.org; **American Legion**, http://www.legion.org; **National Gulf War Resource Center**, http://www.ngwrc.org

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145) 2004-05-03 Perlin JB: Resident Supervision. https://web.archive.org/web/200411041043461/http://www.va.gov/oaa/1400_1hb_May-3-04.doc

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147) 2004-09-16 Andrus CH: "*Primum non nocere"* and practicing ethics in medicine in this era of "the bottom line." U.S. Copyright Office, TXu001203831. https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=7&ti=1,7&Search%5FArg=Andrus%20charles%20h&Search%5FCode=NALL&CNT=25&PID=1oM_rZG-zbNmdQvAShIDo4LwK6mHQOn&SEQ=20210515160330&SID=2

148) 2004-10-07 Andrus CH: Rationing of medical care and the election of 2004. U.S. Copyright Office, TXu001192071. https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=8&ti=1,8&Search%5FArg=Andrus%20charles%20h&Search%5FCode=NALL&CNT=25&PID=4iZ1dm184qpLAbM4gtkZ6Lpi-K68-hK&SEQ=20210515160704&SID=3

Rationing of Medical Care and the Election of 2004

Summer 1999: VA OIG Combine Assessment Program; https://www.va.gov/oig/cap/99-00173-18.pdf

Dr. Thomas Garthwaite, VHA Undersecretary for Health, met at Dr. Garthwaite's request with Dr. Andrus in Atlanta, GA at the AVAS on April 8 & 9, 2001. Three days later after having met with Dr. Andrus, Dr. Garthwaite announced his resignation (but would stay on until January 2002 as the USH) and the official published reason for his resignation was:

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> But Thomas Garthwaite, who had been Kizer's deputy undersecretary, maintained the momentum of the reforms during his tenure as (initially acting) undersecretary between 1999 and 2002. **Garthwaite resigned over disagreements about policy direction with Anthony Principi, the first VA secretary appointed by the Bush administration** (page 22)

Oliver A: The Veterans Health Administration: An American Success Story? The Milbank Quarterly. 2007 Mar; 85(1): 5-35. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

It seemed as though a conjuncture of events very different from those that had opened the window for reform were conspiring against Kizer's leadership. To place Kizer's tenure in context, no undersecretary for health has ever been reconfirmed by the Senate for a second term, and Kizer is the only undersecretary ever to have been renominated by the White House, which indicates that he did still have the support of some senior politicians. Nonetheless, at the end of the nine-month extension of his contract, he resigned.

Leadership that commands great respect is probably quite rare in any large health care organization, and Kizer's departure could have been highly detrimental to the VHA. But Thomas Garthwaite, who had been Kizer's deputy undersecretary, maintained the momentum of the reforms during his tenure as (initially acting) undersecretary between 1999 and 2002. Garthwaite resigned over disagreements about policy direction with Anthony Principi, the first VA secretary appointed by the Bush administration, and was replaced by Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. From then until August 2006, Jonathan Perlin served as undersecretary. Even though it is inevitable that some staff will be dissatisfied with personal leadership styles and no undersecretary will be universally admired, my impression from those with whom I corresponded and interviewed is that the VHA has had at least three able leaders (i.e., Kizer, Garthwaite, and Perlin)

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since the mid-1990s and that their impact on morale and performance, albeit impossible to isolate and quantify, is likely to have been positive.

149) 2004-11-30 Peiris JSM, Guan Y, Yeun KY: Severe acute respiratory syndrome. Nature Medicine Supplement 2004 December; 10(12):S88 – S97. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096017/pdf/41591_2004_Article_BFnm1143.pdf

150) 2004-12-23 Cheng Y, Wong R, Soo YOY, Lee CK, Ng MHL, Chan P, Wong KC, Leung CB, Cheng G: Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7088355/pdf/10096_2004_Article_1271.pdf

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154) 2005-08-20 Andrus CH: Correspondence regarding the manuscript Mortality outcomes and attending surgeon presence at the time of operation. U.S. Copyright Office, TXu001262126 https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=5&ti=1,5&Search%5FArg=Andrus%20charles%20h&Search%5FCode=NALL&CNT=25&PID=49mUgm0LoUN2xjhEZHaERAuUD2qzDv0&SEQ=20210515162031&SID=6

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7088345/pdf/10096_2005_Article_4.pdf

156) 2005-11 Itani KMF, DePalma RG, Schifftner T, Sanders KM, Change BK, Henderson WG, Khuri SF: Surgical resident supervision in the operating room and outcomes of care in Veterans Affairs hospitals. Am J Surg 2005; 190 (5): 725-731.
https://www.americanjournalofsurgery.com/article/S0002-9610(05)00638-0/fulltext

> **"Abstract Conclusions:** Between 1998 and 2004, the level of resident supervision in the OR did not affect clinical outcomes adversely for surgical patients in the VA teaching hospitals. (page 725)"
>
> **Table 1** Levels of attending supervision in the operating room as defined throughout the years of study (page 726)
> 1998-2002 Level 3: attending not present, but available
> 2002-2004 Level 3: attending not present in OR suite, immediately available
> 2004 Level D: attending in OR suite, immediately available
>
> The Abstract Conclusions of "not affect clinical outcomes adversely for surgical patients", were **CONTRADICTED** BY THE VA'S **reported absolute criteria**:
> **Emergency case**, **30-day mortality rate**, and **return to OR**
>
> **Table 4** Intraoperative variables (page 729)

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Intraoperative variables.	Attend 3 (N = 39,577).	All other cases (N = 571,083.	*P* value
Emergency case	12.84% (5,080)	6.79% (38,785).	< .001

Table 5 Unadjusted postoperative outcomes (page 730)

Outcome	Attend 3 (N = 39,577)	All other cases (N = 571,083)	*P* value
30-day mortality rate	2.66% (1,054)	2.34% (13,387)	< .001
30-day morbidity rate.	8.27% (3,274)	10.47% (59,805)	< .001
Return to OR.	10.24% (4,052)	8.19% (46,755)	< .001

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162) 2006-07 Rohrich R: "See One, Do One, Teach One": An old adage with a new twist. Plastic and Reconstructive Surgery, Journal of the American Society of Plastic Surgeons 2006 July; 118(1): 257-258. https://journals.lww.com/plasreconsurg/fulltext/2006/07000/_See_One,_Do_One,_Teach_One___An_Old_Adage_with_a.45.aspx

> The old adage in medicine, "see one, do one, teach one," has changed. It was thought to have served medicine, especially surgery, well over the last century of changes in medical care and medical education, especially when there was no specific or formalized medical training in this country. However, in the new era of American medical compliance (Health Insurance Portability and Accountability Act, patient safety concerns, and compliance oversight),[1] from our various

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professional societies as well as at the state and federal levels, this adage needs to be looked at again and may actually have been detrimental to the patient and the physician's overall well-being.

The days are long gone of residents being unsupervised and teaching other residents on a daily basis. …

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The past seven years have seen a great deal of turmoil in teaching hospitals across the country. Disruptive events in the teaching environment have included the PATH (Physicians at Teaching Hospitals) audits and the resulting expectation for documented faculty presence during procedures, and additional enhanced documentation requirements on faculty and residents. Both have affected the relationship between faculty and residents, and have had a significant impact on the operation of teaching services. A number of our teaching hospitals are safety net institutions, and they have felt tremendous financial pressure. As clinical burdens have increased, faculty time and energy for innovation has been limited. The majority of our teaching hospitals are feeling the burden of the growing uninsured population, the need to provide service to these patients and the escalating needs of the growing population of elderly in the United States. These and many other factors diverted the efforts of the educational community, and slowed the work of innovation in evaluation of physician competency.

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Size of SARS-CoV-2

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December of 2019, many infectious disease specialists, as well as researchers for almost every avenue of medicine, have been investigating how this virus spreads to and infects human beings, the wide range of severe health effects it can cause and ultimately what drugs will be able to effectively kill this virus safely.

In addition to mechanistic information, researchers have also evaluated the size and content characteristics of the SARS-CoV-2 particles. Upon analysis of negative-stained SARS-CoV-2 articles by electron microscopy, different researchers have had varying results, but the diameter of the virus has been found to range between 50 nm to 140 nm.

In addition to measuring the spherical size of the virus particle, it has also been confirmed that the length of the size tumors surrounding the outermost surface of SARS-CoV-2 can vary in length from 9 to 12 nm.

Why does size matter?

Around the world, health officials have agreed that wearing masks can prevent the spread of the virus between individuals. While this may be true, certain masks are considered much more effective at minimizing the risk of exposure, particularly N95 masks.

Whilst N95 masks from different producers may have slightly different specifications, the protective capabilities offered by N95 masks are largely attributed to the masks' obligation to remove at least 95% of all particles with an average diameter of 300 nm or less.

The size of a virus particle largely determines how individuals can protect themselves and those around them from acquiring SARS-CoV-2. Knowing the size of a single virus particle can also allow researchers and healthcare providers to infer the amount of virus individuals are exposed to through different routes.

For example, respiratory droplets are typically 5-10 micrometers (µm) in length; therefore, it can be inferred that an individual who ingests, inhales, or is otherwise exposed to SARS-CoV-2

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positive respiratory droplets can be exposed to hundreds or thousands of virus particles which increases the probability of infection.

Respiratory droplets can be transmitted through coughing, sneezing, contact with contaminated surfaces, or even through inhaled aerosols; therefore, each individual must take adequate steps to reduce their exposure to these particles by wearing masks and practicing safe social distance measures.

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Alexander Pope, poet of the Enlightenment, lent a famous line from his 1711 treatise An Essay on Criticism to the US Institutes of Medicine's report on patient safety: To Err is Human. [1] The remainder of the line, "to forgive divine," would have further reinforced the report's message. Those who made mistakes should neither be blamed nor punished, it argues, instead, to look at the system. …

… Elsewhere in his essay, Pope stresses the many human factors that lead to bad outcomes: overconfidence, tunnel vision, bias, prejudice and inconsistency, among others, and exhorts us to combine "good nature and good sense" in our judgment. …

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> Many years ago, in the Basque country of Spain, there lived a prosperous and generous family who, after feeding family, retainers, and soldiers, had enough to feed even the wild animals. To commemorate this act of generosity, a carving of two wolves eating at a cauldron was placed over the lintel of the family's home in Loyola, Spain.
>
> Many centuries later, St. Ignatius of Loyola would be born into this family and would go on to establish the Jesuit order and change the world. Today, we celebrate this act of generosity, which has become the heraldic shield of the Loyola family, the symbol of this University, and a fitting tribute to our donors, whose generosity makes your education possible at Loyola.

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Also: Epstein NE: Morbidity and mortality conferences: Their educational role and why we should be there. Surgical Neurology International S377-S388. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3520073/pdf/SNI-3-377.pdf

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> **5. RECISSIONS.** VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005 is rescinded……. (page 1). [***Please note that when one searches for VHA Handbook 1400.1, Resident Supervision, dated July 27, 2005, one is redirected to VHA Handbook 1400.01. Using the Wayback Machine and the previous URL for VHA 1400: http://web.archive.org/web/20161221045318/https://www.va.gov/oaa/1400_1hk_Oct2001.doc , one can find the 2001 version in the 2004 of the Internet Archive captures. There are no other captures of this URL in the Wayback Machine except December 21, 2016 which brings up the VA Website which states: "Page Not Found."***
>
> **4. Level D: Attending in OR Suite, Immediately Available.** The supervising practitioner is physically present in the operative or procedural suite and able to provide direct supervision or consultation without delay as needed. (page 9)

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> Arias DC: C. Koop CE—The Nation's Health Conscience. Faces of Public Health. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2253576/pdf/0980396.pdf
>
> "He was a real icon before he even became surgeon general," said Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases and a longtime friend and colleague of Koop.
>
> Koop considered retiring after a trailblazing career that resulted in surgical techniques still used today to save tiny newborns. Yet being tapped to serve as surgeon general at age 64

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excited Koop, who as he approached his 91st birthday, credited his longevity to both genetics and working in a field he adores.

"I've never had a job where I didn't like to get up in the morning and go to it, and that's, I think, unusual," he said from his office at the Koop Institute at Dartmouth. "I told that to a group of medical students a couple of years ago and they looked at me like I was out of my mind."

Known for his powerful speaking voice and trademark beard that have led some to describe him as resembling an Old Testament prophet, Koop likely was such an effective surgeon general because he truly cared about the people he was working to protect. And he doesn't mince words or tiptoe around what some might think of as political land mines.

"He's a completely transparent, honest, tell-it-like-it-is kind of person," said Fauci, once Koop's personal physician and a confidant at the time the surgeon general was working on his controversial AIDS report. "He's just not afraid of anybody."

"This is a man who, above all else, is willing to communicate his convictions with courage when it's the right thing to do," said Timothy Johnson, MD, MPH, medical editor for ABC News and coauthor with Koop of Let's Talk: An Honest Conversation on Critical Issues: Abortion, Euthanasia, AIDS, Health Care. "He's always willing to dialogue and listen to the other side. I think that's a great strength."

… Koop said. "I did a lot of things that I thought were public health, and that stood me in good stead for decisions I had to make. It wasn't nearly the leap that some people think it was or that you might think it is, to go from being a surgeon of individual patients who had a surgical problem to 347 million people, which is what the population was when I went to Washington."

Just before a group of public health luminaries headed to a dessert table to cap off Koop's 90th birthday celebration in Washington, DC, the guest of honor gave an impassioned speech about the need for health care reform. Echoed in a December 2006 Journal editorial,[6] Koop outlined 3 core principles for reform: the fundamental right of all people to have the highest standard of health care, that disparities are "absolutely unacceptable"[1] and at odds with the right to health, and that public, private, and health-related agencies need to make disease prevention and health treatment a priority.

Former Surgeon General Richard Carmona, who served from 2002 to 2006, said Koop brought the office "to a new standard" and was effective because he "stepped up and took risks and did the right thing." Koop said his success can be attributed to a combination of factors.

"I look back on those days, and some things I accomplished because I was naïve. Some things I accomplished because I was furious and I wasn't going to let that stand in my way," Koop said with a smile. "Other things I accomplished by what I call moral suasion . . . and by that I mean having an explanation for what you want to do that transmits the passion you feel for it, the rightness of what you want to do and why it is good for the recipients to have somebody advocate for them because nobody else will."

Those who know Koop well, including Johnson of ABC News, know that the man who hopes to be remembered as "the health conscience of the nation"[2] will work as long as he's able to improve the public's health. "He studies. He knows what he's talking about," Johnson said from his office in New York. "He knows how to say things that will capture your attention."

1990-10-08 Koop, CE: Speech: 'Exasperation on both sides of the stethoscope' American College of Surgeons, San Francisco, CA, October 8,1990.
https://profiles.nlm.nih.gov/spotlight/qq/catalog/nlm:nlmuid-101584930X1005-doc

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THEREFORE, MY MESSAGE TO THE DOCTORS IN AMERICA IS: WHEN YOU ARE DEALING WITH A PATIENT YOU ARE REPRESENTIING ALL OF AMERICAN MEDICINE, YOU ARE REPRESENTING AMERICAN HEALTH CARE.

WE HAVE MUCH TO DO, BUT LET'S NOT LOSE OUR POSITIVE ENERGY.

THE MESSAGE WE HAVE TO SHARE WITH OURSELVES AND WITH THE AMERICAN PEOPLE IS A POSITIVE ONE. WE DON'T NEED THE PAST TENSE,…NOSTALGIA ABOUD THE GOOD OLD DAYS; NOR DO WE NEED SOME FUTURISTIC MANIFESTO PROMISING WHAT WE INTEND TO DO.

WE NEED CLEAR AND PERSISTENT AFFIRMATION OF THE MANY GOOD THINGS WE DO, DAY IN AND DAY OUT, TO MAKE OUR SYSTEM OF MEDICINE—ONCE WE TAKE THINGS IN HAND—POTENTIALLY THE BEST IN THE WORLD.

I HAVE NEVER REGRETED GOING INTO MEDICINE. I'D DO IT AGAIN TOMORROW. AND I TELL THAT TO ANY YOUNGSTERS WHO ARE CONSIDERING IT.

OURS IS A CALLING. IT IS NOT A BUSINESS. WE COULD HAVE MADE MONEY DOING OTHER THINGS.

WE CHOOSE MEDICINE –SURGERY—BECAUSE IT COMBINED A QUESTF FOR KNOWLEDGE WITH A WAY TO SERVE, TO SAY LIVES, AND TO ALLEVIATE SUFFERING.

WE HAVE TO CONVINCE THE PUBLIC WE STILL MEAN IT; IF WE DO, WE'LL GET WHAT WE NEED TO DO THE JOB RIGHT.

I THINK I POSSESS A CERTAIN AMOUNT OF CREDIBILITY, BOTH WITH YOU AND THE GENERAL PUBLIC. I HOPE MY REMARKS TO YOU TODAY DID NOT COST ME SOME OF MY CREDIBILITY WITH SOME OF YOU BECAUSE YOU DON'T LIKE WHAT I SAID. I THINK YOU ALL KNOW THAT MEDICINE IN AMERICA IS IN DEEP TROUBLE, MAYBE AT A TRUE CROSSROADS.

IF YOU DON'T WANT TO SEE US TAKE THE ROAD TO CANADA, OR GREAT BRITAIN, SO SOMETHING NOW. WE MUST DO SOMETHING, SOMETHING TO REKINDLE THE LOVE OF OUR LPROFESSION, THE PRIDE IN LOFTY ETHICS, THE ENJOYMENT OF MEDICINE.

DON'T JUST WRING YOUR HANDS AND GRUMBLE BECAUSE "THEY" HAVEN'T DONE SOMETHING.

YOU ARE THEY.

https://profiles.nlm.nih.gov/spotlight/qq/feature/biographical-overview

….. Through his speeches, publications, and films Koop rose to prominence among anti-abortion activists, and eventually came to the attention of newly-elected president and abortion foe Ronald Reagan, who nominated Koop as U.S. Surgeon General in March 1981. During eight months of controversy and congressional hearings, critics and supporters debated his stance on abortion as well as the question whether Koop, who had devoted his career to treating individual patients, was qualified to address the health needs of the nation as a whole. He was confirmed as U.S. Surgeon General in November 1981.

During his two terms as Surgeon General, Koop made himself the most prominent government spokesman on issues affecting the health of the American public, despite having little statutory authority and a small budget. He infused a renewed sense of confidence and purpose into the Commissioned Corps of the U.S. Public Health Service (PHS), a federal service of public health professionals that the Surgeon General commands and that had been suffering from low morale after the closing of PHS hospitals and the cut-back in personnel in the early 1980s. He examined medical ethics,

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health care costs, and the problem of the uninsured in a health care system that faced financial challenges at a time of inflation followed by recession in the early 1980s. …

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215) 2013-12-11 Mamede S, Schmidt HG: The twin traps of overtreatment and therapeutic nihilism in clinical practice. ASME Medical Education 2014 Jan; 48(1): 34-43. https://onlinelibrary.wiley.com/doi/10.1111/medu.12264

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217) 2014-03 Gesensway D: Ducking out early? https://www.todayshospitalist.com/ducking-out-early/

218) 2014-06-28 Teixeira JLG, Rabaioli P, Savaris RF: Sensitivity and specificity of a urinary screening test used in an emergency setting to detect abnormal trimester pregnancies. Am J Obstetrics & Gynecology, Research Gynecology 2014 June 28; 212 (1). https://www.ajog.org/article/S0002-9378(14)00636-X/pdfSummary

219) 2014-09 World Health Organization: Use of convalescent whole blood or plasma collected from patients recovered from ebola virus disease for transfusion, as an empirical

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221) 2015 World Health Organization: Ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic. https://apps.who.int/iris/bitstream/handle/10665/161912/WHO_HIS_KER_GHE_15.1_eng.pdf;jsessionid=D65658E684B1899A98FC90E389B4A6A0?sequence=1

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224) 2015-02-04 Gaffney A: From 100 hours to 1: FDA dramatically simplifies its Compassionate Use Process. VERISTAT https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2015/2/from-100-hours-to-1-fda-dramatically-simplifies-its-compassionate-use-process

225) 2015-06 Triulzi D, Gottschall J, Murphy E, Wu Y, Ness P, Kor D, Roubinian N, Fleischmann D, Chowdhury D Brambilla D, and for the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). A multicenter study of plasma use in the United States. HHS Public Access, Transfusion 2015 June; 55 (6): 1-17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4968201/pdf/nihms777310.pdf

226) 2015-08-10 van Griensven J, De Weiggheleire A, Delamou A, Smith PG, Edwards T, Vandekerckhove P, Ibrahima Bah E, Colebunder R, Herve I, Lazaygues C, Haba N, Lynen L: The use of Ebola convalescent plasma to treat Ebola virus disease in resource-constrained settings: A perspective from the field. Clinical Infectious Diseases (IDSA) https://academic.oup.com/cid/article/62/1/69/2462604 (Controversial but recommend further studies)

227) 2015-08-22 Pellegrini C: Robert Condon MD FACS 1929-2015: In Memory. World J Surg 2015; 39: 2611-2612. https://www.readcube.com/articles/10.1007%2Fs00268-015-3226-y

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

228) 2015-09-17 HHS.gov, U.S. Department of Health and Human Services: What is the cost for getting records under the FOIA? https://www.hhs.gov/foia/faqs/what-is-the-cost-for-getting-records-under-the-foia/index.html

While the website above the generalities, to submit FOIA request is somewhat complicated and the following disclaimer for the NIH—National Institutes of Health in part is: …Please submit all requests through our online portal (link below) rather than mail, fax, or courier, to ensure timely logging of your requests….

First (1): https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/freedom-information-act-office/submitting-foia-requests

Next (2): click on the Submit a FOIA Request:

Next (3): The following disclaimer will show up which after reading it, if one wishes to proceed, you should click on "I Accept":

You are about to access a United States Government computer system. This information system is provided for U.S. Government-authorized use only. Unauthorized or improper use of this system may result in disciplinary action, as well as civil and criminal penalties.

By using this information system, you understand and consent to the following:

- You have no reasonable expectation of privacy regarding any communication or data transiting or stored on this information system. At any time, and for any lawful Government purpose, the government may monitor, intercept, and search and seize any communication or data transiting or stored on this information system.

- Any communication or data transiting or stored on this information system may be disclosed or used for any lawful Government purpose.

No particular form is prescribed for making a FOIA request. You may submit a FOIA request using the NIH FOIA Request Portal or in any manner that conforms to the HHS FOIA regulations. http://www.hhs.gov/foia/statutes-and-resources/45cfr5/index.html

Privacy Act Statement

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This Statement is provided pursuant to the Privacy Act of 1974 (5 U.S.C. § 552a): The information you are requested to provide in order to use the NIH FOIA Request Portal is authorized to be collected under the Freedom of Information Act (5 U.S.C. § 552). Completing the request portal fields is voluntary, but failing to provide any or all of the requested information may prevent HHS from creating a portal account for you, or may prevent HHS from processing your request. The principal purposes for which HHS will use the information that you provide in the NIH FOIA Request Portal are to create an account for you, and to track, process, and respond to requests that you submit to HHS through your account. The information you provide will be included in a Privacy Act system of records, and will be used and may be disclosed for the purposes and routine uses described and published in the following System of Records Notice (SORN): 09-90-0058 Tracking Records and Case Files for FOIA and Privacy Act Requests and Appeals https://www.federalregister.gov/articles/2016/03/29/2016-07060/privacy-act-of-1974-system-of-records-notice
https://www.congress.gov/114/bills/s337/BILLS-114s337enr.xml

https://www.justice.gov/oip/freedom-information-act-5-usc-552

All requests received after 5 pm Eastern Time, will be considered "received" on the next business day.

Next (4): You will then be electronically directed to: The NIH Website for submissions.

Next (5) When you actually submit the prose of your request, you should request:

NIAID Case #12276
NIH National Institute of Allergy and Infectious Diseases

Which was opened on June 10, 2020 in which the correspondence stated: "…Due to his professional responsibilities, Dr. Fauci has asked me to respond on his behalf."

By:
Kara M. Harris, MPH
Section Chief for Controlled Correspondence and Public inquires
Legislative Affairs and Correspondence Management Branch
Office of Communications and Governmental Relations
National Institute of Allergy and Infectious Diseases
National Institutes of Health

After reviewing Dr. Fauci's *White House* slide show on Monoclonal Antibodies of August 24, 2021, 10:30 to 15:27 minutes on the URL, I called Ms. Harris's office on 8/30/2021 leaving a message requesting that Dr. Fauci call me. In a phone response to my phone call (my VA office phone number is: 314-652-

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4100 ext 54463), "Meg" who identified herself from Ms. Harris's office responding for their office stated that all the information I had submitted had been forwarded to the appropriate divisions. I then pleaded my case with "Meg" who patiently listened for about twenty minutes. Finally, when she stated she needed to go, she stated in her parting comments that she assured me that they still had all the information I had submitted in NIAID Case #12276. **Thus, under FOIA, all in NIAID Case #12276 should be available to anyone properly requesting it under Federal Law.**

[Please note Dr. Fauci's opening comments in his *White House* slide show:
https://www.youtube.com/watch?v=AZNP05w2cxU

DR. FAUCI: Thank you very much, Dr. Walensky. I'd like to spend the next couple of minutes in addressing a **much-underutilized intervention for COVID-19, and that is the use of monoclonal antibodies for the TREATMENT** and **PREVENTION of SARS-CoV-2 infection and COVID-19 disease**.

Next slide.

For those not totally familiar with this, monoclonal antibody is an antibody that's produced by a single clone of B cells or a cell line, and consists of identical antibody molecules that can actually be produced in the in-vitro situation in unlimited quantities.

Next slide.

If you look at the virion on the upper-left part of the slide and you look up the blown-up spike protein — the red molecule on the right upper panel — **when you talk about polyclonal antibodies, which result from infection or vaccination, it's a group of antibodies against every aspect of the spike protein, which is the good news. However, the concentration and the affinity of those antibodies can be markedly improved if you get a single cloned antibody — hence the word "monoclonal" — that's against the very specific part of the spike protein that can have a major effect in prevention and treatment. …]**

229) 2015-12 In Memoriam—Robert Condon, MD. University of Washington Medicine, Surgery Synopsis 2015 Winter; 20 (1): 13. http://uwsurgery.org/images/site/synopsis/vol20issue1/SurgSynopsis_Wtr2015_FINAL.pdf

230) 2015-12 Metcalf CJE, Ferrari M, Graham AL, Greenfell BT: Understanding herd immunity. Trends Immunol 2015 Dec; 36(12): 753-755. https://kilpatrick.eeb.ucsc.edu/wp-content/uploads/2013/04/Metcalf-et-al-2015-Trends-Immuno.pdf

231) 2015-12-15 Sorensen CG, Karlsson WK, Pommergaard HC, Burcharth J, Rosenberg J: The diagnostic accuracy of carcinoembryonic antigen to detect colorectal cancer recurrence –

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

A systematic review. International J Surg 2016; 25: 134-144. https://reader.elsevier.com/reader/sd/pii/S1743919115013953?token=49DCDCBEC5D356E472B0294B3D7F4B231DFE55987BBD7FEA43A5361DE5C847EA36A55F844D18C0A6FA74A965B3A3979B&originRegion=us-east-1&originCreation=20220416013146

232) 2016 Marano G, Vaglio S, Pupella S, Gacco G, Catalano L, Liumbruno GM, Grazzini G: Convalescent plasma: new evidence for an old therapeutic tool? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4781783/pdf/blt-16-152.pdf

233) 2016-02-25 Shander A, Ozawa S, Hofmann: Activity-based costs of plasma transfusions in medical and surgical inpatients at a US hospital. VoxSanguinis. https://onlinelibrary.wiley.com/doi/full/10.1111/vox.12386

234) 2016-03-24 Freischlag JA: Bouncing Up: Resilience and women in academic medicine. Olga M Jonasson lecture. J America College of Surgeons https://www.readcube.com/articles/10.1007%2Fs00268-015-3226-y

235) 2016-04-03 Ball P: The truth about Hannibal's route across the Alps. The Guardian https://www.theguardian.com/science/2016/apr/03/where-muck-hannibals-elephants-alps-italy-bill-mahaney-york-university-toronto

236) 2016-05-01 Graham BS, Ambrosino DM: History of passive antibody administration for prevention and treatment of infectious diseases. Curr Opin HIV AIDS 2015 May; 10(3): 129-134. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4437582/

237) 2016-06-02 NEJM Knowledge+ Team: Exploring the ACGME Core Competencies (Part 1 of 7). https://knowledgeplus.nejm.org/blog/exploring-acgme-core-competencies/

> Exploring the ACGME Core Competencies: (Part 1 of 7) https://knowledgeplus.nejm.org/blog/exploring-acgme-core-competencies/
>
> Exploring the ACGME Core Competencies: Practice-based learning and improvement (Part 2 of 7) https://knowledgeplus.nejm.org/blog/practice-based-learning-and-improvement/
>
> Exploring the ACGME Core Competencies: Patient Care and Procedural Skills (Part 3 of 7) https://knowledgeplus.nejm.org/blog/patient-care-procedural-skills/
>
> Exploring the ACGME Core Competencies: Systems-Based Practice (Part 4 of 7) https://knowledgeplus.nejm.org/blog/acgme-core-competencies-systems-based-practice/
>
> Exploring the ACGME Core Competencies: Medical Knowledge (Part 5 of 7) https://knowledgeplus.nejm.org/blog/acgme-core-competencies-medical-knowledge/
>
> Exploring the ACGME Core Competencies: Interpersonal and Communication Skills (Part 6 of 7) https://knowledgeplus.nejm.org/blog/acgme-core-competencies-interpersonal-and-communication-skills/

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Prevention: *Active Immunization*: Vaccines

Exploring the ACGME Core Competencies: Professionalism (Part 7 of 7)
https://knowledgeplus.nejm.org/blog/acgme-core-competencies-professionalism/

238) 2016-07 Gupta KK, Attri JP, Singh A, Kaur H, Kaur G: Basic concepts for sample size calculation: Critical Step for any clinical trials! Saudi J Anaesth 2016 Jul-Sep; 10 (3): 328-331. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916819/pdf/SJA-10-328.pdf

239) 2016-08-09 Behrns KE: *Curriculum vitae* of Kevin E. Behrns, M.D., F.A.C.S., co-editor-in-chief of *Surgery*. https://com-surgery-main.sites.medinfo.ufl.edu/files/2016/08/View-Kevin-Behrns-curriculum-vitae.pdf

In July 2020, Dr. Behrns was a General Surgeon of the Department of Surgery, Saint Louis University School of Medicine; co-Editor-in-Chief of *Surgery*; and was a fellow faculty member in General Surgery Division, Department of Surgery, Saint Louis University School of Medicine of Saint Louis University and shared the General Surgery outpatient offices with me on Friday mornings. Knowing that he had graduated from the Mayo Clinic Medical School and had been a Surgery resident and researcher at the Mayo Clinic in the 1990's, I requested of him that he contact Michael Joyner, M.D., the Principal Investigator for the Mayo Clinic / FDA Expanded Access program for COVID-19 Convalescent Plasma. Dr. Joyner responded with a brief e-mail response to Dr. Behrns:

Having a lot of trouble with USG.

By that time in July 2020, I had submitted to the offices of Dr. Fauci, Dr. Hahn, and President Trump multiple communications regarding *Passive Immunization treatment* with COVID-19 Convalescent Plasma which had been included in my submissions 1.) to the U.S. Copyright Office to be preserved for history in the Library of Congress and 2.) had been included in NIH NIAID case #12276:

1. Andrus CH: ***Time:*** The Crucial *Independent* Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029. https://web.archive.org/web/20210904014401/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=9&ti=1%2C9&Search_Arg=Andrus+Charles+H&Search_Code=NALL&CNT=25&PID=DvTGOW_Qvd_foYxTFrVcdewL3ktMCwz&SEQ=20210425193720&SID=1

2. Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049. https://web.archive.org/web/20210904020833/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=6&ti=1%2C6&Search_Arg=andrus+charles+h&Searc

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h_Code=NALL&CNT=25&PID=cXfFuGrmHQvLVlLvfNNt7Yjwh73ImgQ&SEQ=20210512081428&SID=1

Dear Mr. President, please note that all information I have submitted over the last two years to Dr. Fauci was directed by Dr. Fauci to be dealt with by:

Kara M. Harris, MPH
Section Chief for Controlled Correspondence and Public Inquires
Legislative Affairs and Correspondence Management Branch
Office of Communications and Governmental Relations
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Per her letter of June 10, 2020, Ms. Harris assigned my correspondence with Dr. Fauci's office to NIAID Case #12276 and I have continued to submit my correspondence addressed with Dr. Fauci's office for the last two years labelled in the heading: NIAID Case#12276. After reviewing Dr. Fauci's *White House* slide show on Monoclonal Antibodies of August 24, 2021, 10:30 to 15:27 minutes on the URL, *I called Ms. Harris's office on 8/30/2021 leaving a message requesting that Dr. Fauci call me. In a phone response to my phone call (my VA office phone number is: 314-652-4100 ext 54463), "Meg" who identified herself from Ms. Harris's office responding for their office stated that all the information I had submitted had been forwarded to the appropriate divisions. I then pleaded my case with "Meg" who patiently listened for about twenty minutes. Finally, when she stated she needed to go, she stated in her parting comments that she assured me that they still had all the information I had submitted in NIAID Case #12276.* **Thus, under the Freedom of Information Act (FOIA), all in NIAID Case #12276 should be available to anyone properly requesting it under Federal Law.**

Mr. President, please excuse my digressing from Dr. Joyner's e-mail response to Dr. Behrns of: **Having a lot of trouble with USG. Mr. President**, could you please excuse the 'expletives' (E!) that I will include in my discussion that follows because over the course of the last two years the American people (and the World) have been misled, misinformed, and lied to (E!) regarding major issues of treatment of COVID0=19 by agencies of the Federal Government (e.g., FDA, NIH, CDC, PHS, VA, etc.), spokespersons of Organized / Academic Medicine (e.g.: *The New England Journal of Medicine)*, and the Biological and Pharmaceutical industries assisted by B.A.R.D.A., other research agencies like DARPA, etc.

After Dr. Behrns voiced Dr. Joyner's e-mail response of ***"having a lot of trouble with USG"*,** Dr. Behrns questioned me as to who was **USG**? My response was simple: **USG** is the **United States Government**; and Dr. Joyner was referring off-handedly to a nebulous but responsible/accountable **USG**. I then explained that the **USG** had so *screwed up* (E!) that "they" didn't know how to get out of the rabbit hole.

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240) 2016-09-27 U.S. Federal Register: Clinical Trials Registration and Results Information Submission. A Rule by the Health and Human Services Department on 09/21/206. Phase I meaning in 21 CFR 312.21. https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission USC 312.21 https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-B/section-312.21

241) 2016-10-11 Blavin F: Association between the 2014 Medicaid expansion and US hospital finances. JAMA 2016 Oct 11; 316 (14): 1475 -1483. https://jamanetwork.com/journals/jama/fullarticle/2565750

242) 2016-12-22 Veterans Health Administration, Research & Development: Milestones in VA-Academic Collaboration. https://www.research.va.gov/researchweek/press_packet/Collaboration.pdf

243) 2017 American College of Surgeons: The evolution of the Fellowship Pledge. https://www.facs.org/about-acs/archives/pasthighlights/pledge

244) 2017-01-12 Keown A: Trump says pharma getting away with murder, vows to lower drug prices. Biospace.com https://www.biospace.com/article/-b-trump-b-says-pharma-getting-away-with-murder-vows-to-lower-drug-prices-/

245) 2017-01-28 U.S. National Institutes of Health, U.S. Department of Health and Human Services: NIH policy on the dissemination of NIH-funded clinical trial information. Notice Number: NOT-OD-16-149, Release Date: September 16, 2016, Effective Date: January 18, 2017. https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html

246) 2017-01-31 Georgetown Preparatory School: The Honorable Neil Gorsuch ’85 nominated to serve on the U.S. Supreme Court. https://www.gprep.org/about/news/~post/the-honorable-neil-gorsuch-85-nominated-to-serve-on-the-us-supreme-court-20170131

247) 2017 Keusch G, McAdam K, Cuff PA, Mancher M, Busta ER, Committee on Clinical Trials during the 2014-2015 Ebola outbreak. A Report of *The National Academies of* SCIENCES, ENGINEERING, MEDICINE. https://www.ncbi.nlm.nih.gov/books/NBK441679/pdf/Bookshelf_NBK441679.pdf

248) 2017-02-03 McGough M: Opinion: Neil Gorsuch was a teenage wisenheimer, not a teenage fascist. LA Times https://www.latimes.com/opinion/opinion-la/la-ol-gorsuch-fascist-20170203-story.html

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249) 2017-03 Rogers T, Zeckhauser R, Gino F, Norton MI, Schweitzer: Artful paltering: The risks and rewards of using truthful statements to mislead others. J Per Soc Psychol 2017 Mar; 112(3): 456-473. https://pubmed.ncbi.nlm.nih.gov/27936834/

250) 2017-05 FDA: Scott Gottlieb M.D., Commissioner of Food and Drugs - Food and Drug Administration (May 2017 – April 2019. https://www.fda.gov/about-fda/fda-leadership-1907-today/scott-gottlieb

Pfizer: Scott Gottlieb, M.D., Board Member. https://www.pfizer.com/people/leadership/board_of_directors/scott_gottlieb-md

251) 2017-05-08 Taylor NP: Celgene, Regeneron and Vertex execs, NIH chief head to White House as threat of Trump funding cuts looms. Fierce Biotech https://www.fiercebiotech.com/biotech/celgene-regeneron-and-vertex-execs-nih-chief-head-to-white-house-as-threat-trump-funding

252) 2017-05-16 History Channel: Tuskegee Experiment: The Infamous Syphilis Study. https://www.history.com/news/the-infamous-40-year-tuskegee-study

253) 2017-05-16 Brown DL: 'You've got bad blood': The horror of the Tuskegee syphilis experiment. The Washington Post https://www.washingtonpost.com/news/retropolis/wp/2017/05/16/youve-got-bad-blood-the-horror-of-the-tuskegee-syphilis-experiment/

254) 2017-07-28 Issa LA, Noureddine M: Colorectal cancer screening: An updated review of the available options. World J Gastroeterol 2017 Jul 28; 23 (28): 5086-5096. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537177/

255) 2017-08-11 Blakemore Erin: How America's most powerful men caused America's deadliest flood. History channel https://www.history.com/news/how-americas-most-powerful-men-caused-americas-deadliest-flood

256) 2017-10 Tan SY, Merritt C: Charles Richard Drew (1904-1950): Father of blood banking. Singapore Med J 2017; 58 (10): 593 – 594. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5651504/pdf/SMJ-58-593.pdf

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- The Red Cross begins National Blood Donor Service to collect blood for the U.S. military with Dr. Charles R. Drew, formerly of the Plasma for Britain program, as medical director.
- Soldiers injured during the Pearl Harbor attack are treated with albumin for shock

https://www.redcrossblood.org/donate-blood/blood-donation-process/what-happens-to-donated-blood/blood-transfusions/history-blood-transfusion.html

https://www.pbs.org/newshour/science/desegregating-blood-a-civil-rights-struggle-to-remember

https://www.universitybloodinitiative.org/post/blood-donation-and-race-series-the-historic-segregation

257) 2017-11 Reines HD, Trickey AW, Donovan J. Morbidity and mortality conference is not sufficient for surgical quality control: Processes and outcomes of a successful attending physician peer review committee. Am J Surg 2017 Nov; 214 (5): 780-785. https://www.americanjournalofsurgery.com/article/S0002-9610(16)30526-8/fulltext

258) 2018 Slifka MK, Amanna IJ: Passive immunization. Plotkin's Vaccines 2018: 84-95. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151993/pdf/main.pdf

259) 2018-01-04 FDA What are the different types of clinical research? https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research

NIH, National Institutes of Health: Glossary of Common Terms. https://www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms

260) 2018-01-29 STS Press Release: Keith S. Naunheim elected President of The Society of Thoracic Surgeons – Saint Louis University surgeon will focus on health care delivery and reimbursement. https://www.sts.org/sites/default/files/press-releases/President%20release_Naunheim_FINAL_FMT.pdf

Over the years, in Dr. Naunheim's discussions of many articles in the literature, he has pointed out to the Saint Louis University students, residents, and faculty the always-possible inherent potential skewing of a statistical analysis by excluding a large number of individuals (e.g.: infected, cancer positive, non-control individuals, etc.) from a prospective Randomized Controlled Trials (RCT) until the decreasing denominator renders the RCT underpowered and useless. He has often referred to this as: *"The Amazing Shrinking Denominator."* The reference that follows entitled: Koehsen W: Lessons on how to lie with statistics – Timeless data literacy advice. https://towardsdatascience.com/lessons-from-how-to-lie-with-statistics-

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Prevention: *Active Immunization*: Vaccines

57060c0d2f19 is analogous to Dr. Naunheim's expression of *"The Amazing Shrinking Denominator"*:

> Scientists are usually limited to small samples by legitimate problems, but advertisers use small numbers of participants in their favor by conducting many tiny studies, one of which will produce a positive result. Humans are not great at adjusting for sample sizes when evaluating a study which in practice means we treat the results of a 1000 person trial the same as a 10 person trial. **This is known as "insensitivity to sample size" or "sample size neglect".**

261) 2018-02-22 Neighbor J: RhoGAM at 50: A Columbia drug still saving lives of newborns – RhoGAM, a drug developed in the 1960s by Columbia University physicians, prevents one of the most severe and devastating diseases affecting fetuses and newborn babies and is still in use today. Columbia University Irving Medical Center. https://www.cuimc.columbia.edu/news/rhogam-50-columbia-drug-still-saving-lives-newborns

262) 2018-03-01 Yan F, Thall PF, Lu KH, Gilbert MR, Yuan Y: Phase I-II clinical trial design: a state-of-the-art paradigm for dose finding. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5888967/pdf/mdx795.pdf

263) 2018-03-05 FDA: Vaccinia Immune Globulin Intravenous. https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/vaccinia-immune-globulin-intravenous-human

VIGI (Human) Package insert: https://www.fda.gov/media/77004/download

VIGIV (Human) Package insert: https://www.fda.gov/media/78174/download

264) 2018-03-09 De Geest BG: Engineering the immune system with particles, step-by-step. Molecular Immunology 2018; 98: 25-27. https://www.sciencedirect.com/science/article/abs/pii/S0161589018300452?via%3Dihub

265) 2018-03-20 McKinley JC: President Trump must face accusations of 'Apprentice' contestant. The New York Times. https://www.nytimes.com/2018/03/20/nyregion/trump-defamation-lawsuit-new-york-summer-zervos.html

266) 2018-04-03 Mintz S: Do the Ends Justify the Means? Ethics Sage. https://www.ethicssage.com/2018/04/do-the-ends-justify-the-means.html

267) 2018-04-04 Zhu Z, Zhang Z, Chen W, Cai Z, Ge X, Zhu H, Jiang T, Tan W, Peng Y: Predicting the receptor-binding domain usage of the coronavirus based on kmer frequency on spike protein. Infection, genetics and evolution 2018; 61: 183-184. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129160/pdf/main.pdf

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

268) 2018-04-19 Marston HD, Paules C, Fauci AS: Monoclonal antibodies for emerging infectious diseases – Borrowing from history. N Engl J Med 2018 Apr 19; 378 (16): 1469 – 1472. https://www.nejm.org/doi/10.1056/NEJMp1802256?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

In the NEJM Managing Editor's interview of Dr. Fauci regarding this publication, Dr. Fauci laid out the exact same discussion and advocacy for early treatment of novel viruses with monoclonal antibodies *8 months before* SARS-CoV-2 was even seen or identified on this earth!: Morrissey S, Fauci A: Interview with Dr. Anthony Fauci on the use of monoclonal antibodies in the context of emerging infectious diseases. Supplement to the N Engl J Med 2018; 378: 1469-1472. (Mr. President, **please listen** to this five minute interview after reviewing Dr. Fauci's youtube slide presentation and discussion of the August 24, 2021 White House briefing (minutes 10:30 to 15:25): https://www.youtube.com/watch?v=AZNP05w2cxU.

The hyperlink for the 2018 NEJM Morrissey interview of Dr. Fauci is:
https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area=

Dr. Morrissey:

Although there is a long history of plasma derived treatments for several pathogens, only a handful of antibody therapies have been licensed for infectious diseases. But recent advances in the development of monoclonal antibodies could have important implications for our response to infectious disease outbreaks. I'm Stephen Morrissey, Managing Editor of the New England Journal of Medicine, and I am talking with Anthony Fauci, Director of the National Institute of Allergy and Infectious diseases. Dr. Fauci has coauthored a prospective article about the promise of monoclonal antibodies for rapid intervention during infectious disease outbreaks. Dr. Fauci: What are the primary benefits of using monoclonal antibodies for prevention and treatment infectious diseases? What advantages do they have over current approaches?

Dr. Fauci:
Well, one of the things that got us to be very interested in that is just that potential advantage. Namely, that when you have to respond, for example, to an unexpected outbreak of an infectious disease, one of the major tools against that to control it or hopefully eliminate it is development of a safe and effective vaccine. The problem with that is that the time that it takes, even when you put it on a rapid pace, the time that it takes to get a vaccine that you show to be safe and effective often falls behind and lags dramatically behind the actual outbreak itself. Whereas if you can with our techniques that we have right now which of greatly improved over the past several years to isolate and develop monoclonal antibody specific to the agent in question--you can use it much more rapidly. Obviously there's the issue of being able to scale up, but you get a monoclonal antibody in hand soon after you're confronted with an outbreak has a major advantage over the long time-honored but nonetheless rather drawn out process of developing a vaccine.

Dr. Morrissey:
You write in your article that several antibody therapies have been licensed for infectious diseases. What have researchers learned from the development of those therapies and for more recent attempts to create monoclonal antibodies against—say-- Ebola or Zika?

Dr. Fauci:

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Well, for example, a classic monoclonal antibody for prophylaxis against Respiratory Syncytial Virus has been developed with considerable success. We began thinking very intensively about this just literally over the past few years when we in rapid succession had to confront both the Ebola outbreak followed by the Zika outbreak. And it became very clear that during the Ebola outbreak that there were monoclonal antibodies in the form of ZMapp that was able to actually have an impact even though we did not have the opportunity of doing a very large clinical trial. We did show that there was clearly a tendency towards a benefit of this cocktail of three mouse human chimeric antibodies against Ebola, that we felt that this particular approach if perfected both in the development and scale-up of these antibodies might have an important role in future outbreaks. So, we're thinking that this is going to be something, and including for example influenza, so there have been now a couple of monoclonal antibodies that have been made against influenza. And when you think in terms of a threat of a pandemic influenza and you would want to get an antibody that would be effective in neutralizing a brand new virus well before the time it takes to develop the vaccine, here again is something that we're going to be pursuing and are pursuing at the present time.

Dr. Morrissey:
So how do you envision that process of developing new antibody therapies during an outbreak?

Dr. Fauci:
There a couple of ways of doing that. Probably the easiest way, because the technology now is so sophisticated, is to get an individual who has been infected with whatever pathogen is the one behind the outbreak. And because of the ability now to clone the B cells from the B cell repertoire and essentially fish out—and, truly metaphorically fishing-out the right B cell clones that have the specificity that you are thinking about and wanting to develop and immediately get those to be cloned, sequenced, and then the development of a high through-put process to give you monoclonal antibodies. That's something that was unheard of years ago—literally unheard of where you can actually probe and interrogate the B cell repertoire and the B cell lineage of a person who has recovered from the infection in question; and use those B cells as the source of the monoclonal antibody in question. And that's something that could be done immediately, and from the standpoint of the process of it, to be done very rapidly. So you can envision an outbreak where you have right-away, the sentinel people you have clearly getting sick from the pathogen you have in question and as they recover you just draw some blood from them and you can pull out with the techniques we have a variety of B cell clones that have various specificities and then you can test in vitro what is the best, what has the highest affinity, what is the most specific, what are the epitopes involved, and then start using them for both diagnosis, prophylaxis, and for treatment.

Dr. Morrissey
You talk in your article about the current high cost of production and complexity of administration of these monoclonal antibodies. So how great a limitation is that and do you foresee a time when those issues will be less of a barrier than they are now?

Dr. Fauci:
Well, that's a great question, and I'd have to answer totally, honestly—that it is a barrier that is substantial right now at present. But as we've done with so many other things that we've been able, we in the field, not me personally, but we in the field have been able to develop over years--is that once you get the first step namely the specificity, the effectiveness of a particular antibody, then you work on the development of scale-up. But the idea of scaling up at a reasonable cost where these antibodies can be used widely

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is a challenge. But I do believe that as we get better and better at it as we have with other technologies that have started off to be very cumbersome and very expensive, I believe over time when there is accelerated interest in this approach which I believe there will be that we will be able to overcome that barrier of the ability to produce at a high degree.

Dr. Morrissey:
In your article, you describe three indications for monoclonal antibodies: the treatment of infected individuals, targeted prophylaxis to protect high-risk individuals, and targeted prophylaxis to interrupt transmission in populations at average risk. So which of these strategies do you think has the most potential to halt the spread of an epidemic?

Dr. Fauci:
Well, clearly if you are talking about halting the spread of an epidemic, the last two that you mentioned because the first one is the treatment of an infected individual. Now obviously you can say well treatment will turn out to be prevention because if you treat a particular person they may not transmit it to another; but I think the much more efficient way of preventing the expansion of an outbreak is the targeted prophylaxis either directly at high risk individuals or even at a population level to prophylaxis and interrupt transmission in people who are at average risk and that is really what we talk about in interrupting the chain of transmission. So, if you have an influenza outbreak, you may be able to use this as prophylaxis before you get a vaccine that is available to essentially have a more population-based prevention. So, I believe the high risk individuals that are targeted for prophylaxis is going to be a very important way to interrupt certain outbreaks regardless of what the source of that outbreak is.

Dr. Morrissey:
Finally, what will it take to increase our interest in our investment in the use of monoclonal antibodies for infectious diseases? What, for example, is NIAID doing?

Dr. Fauci:
Let me answer your question broadly, then I will get back to the specific of what we are doing. Really nothing succeeds like success as they say. Once you start demonstrating the effectiveness of this approach in different outbreaks—and we have seen inklings of this with the ZMapp approach to Ebola with some of the monoclonal antibodies—all-be-it in the animal models with Zika, they worked very well in the animal models to prevent the transmission of the virus to a fetus in an animal model; and thus prevented the congenital defects in this animal model. I believe that when we get to the point of testing it in humans, under these circumstances, we will see similar success. So, that is what I mean by nothing succeeds like success once you have a few examples of successful application of this particular approach. You are going to get a lot more interest in it. What we at NIH are doing is what we do most of the time is these types of approaches; and that is, to do the basic and clinical research to get this developmental process to be quick and to be effective. We done that and it ranges all the way from the fundamental basic research on B cell lineage--that really led to the ability to develop monoclonal antibodies at a high degrees of specificity and the high degree of ability to neutralize whatever a particular pathogen you have in question. So, the NIH ‘s job will be what we have been doing all a long, is the fundamental basis to give clinical research leading to the application of these types of interventions.

Dr. Morrissey:
Thank you, Dr. Fauci.

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269) 2018-05-08 NIH, NIAID: H. Clifford Lane, M.D., NIAID Deputy Director, Clinical Research and Special Projects, Director, Division of Clinical Research. https://www.niaid.nih.gov/about/h-clifford-lane-md-bio

270) 2018-05-30 President Trump signed into law PL-115-176: Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina, the RIGHT TO TRY ACT OF 2017. https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf

What is on the following pages is a copy of Public Law 115-176. As is stated in **SEC. 561 B. INVESTIGATIONAL DRUGS FOR USE BY ELIGIBLE PATIENTS**, (a), (2)the term 'eligible investigational drug' means an investigational drug (as such term is used in section 561)—(A) for which a Phase 1 clinical trial has been completed; (B) that has not been approved or licensed for any use under section 505 of this Act or section 351 of the Public Health Service Act; **Throughout** the COVID-19 Pandemic over the last 16 months, the FDA and the NIH in all announcements, policy statements, etc. have equated ***safety*** with ***efficacy***—**WHICH IS A MISINTERPRETATION OF PL-115-176.** Distinctly by FDA and NIH definitions, **Phase 1 clinical trials** are **SAFETY** clinical trials while **Phase 2 and 3 clinical trials** are **EFFICACY** clinical trials. In short, when a **Phase 1 clinical trial** is deemed "Completed" by the FDA, the *Investigational* drug or biologic should be available to all individuals who have contracted a potentially terminal disease like COVID-19 under PL-115-176 until the FDA designates a New Drug Authorization number making the drug or biologic non-investigational and thus available to all. By the FDA NOT "officially" declaring "Completed" Phase 1 clinical trials for any of the ***Passive Immunization agents*** and by RADM Denise Hinton, R.N., M.S. issuing Emergency Use Authorizations (EUA) for all ***Passive Immunization agents***, all ***Passive Immunization agents*** are **ALL** *INVESTIGATIONAL* at present time.

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Public Law 115–176
115th Congress

An Act

May 30, 2018
[S. 204]

To authorize the use of unapproved medical products by patients diagnosed with a terminal illness in accordance with State law, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.
21 USC 301 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017".

SEC. 2. USE OF UNAPPROVED INVESTIGATIONAL DRUGS BY PATIENTS DIAGNOSED WITH A TERMINAL ILLNESS.

(a) IN GENERAL.—Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by inserting after section 561A (21 U.S.C. 360bbb–0) the following:

21 USC 360bbb–0a.

"SEC. 561B. INVESTIGATIONAL DRUGS FOR USE BY ELIGIBLE PATIENTS.

"(a) DEFINITIONS.—For purposes of this section—

"(1) the term 'eligible patient' means a patient—

"(A) who has been diagnosed with a life-threatening disease or condition (as defined in section 312.81 of title 21, Code of Federal Regulations (or any successor regulations));

"(B) who has exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug, as certified by a physician, who—

"(i) is in good standing with the physician's licensing organization or board; and

"(ii) will not be compensated directly by the manufacturer for so certifying; and

"(C) who has provided to the treating physician written informed consent regarding the eligible investigational drug, or, as applicable, on whose behalf a legally authorized representative of the patient has provided such consent;

"(2) the term 'eligible investigational drug' means an investigational drug (as such term is used in section 561)—

"(A) for which a Phase 1 clinical trial has been completed;

"(B) that has not been approved or licensed for any use under section 505 of this Act or section 351 of the Public Health Service Act;

"(A) for which a Phase 1 clinical trial has been completed;

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"(C)(i) for which an application has been filed under section 505(b) of this Act or section 351(a) of the Public Health Service Act; or

"(ii) that is under investigation in a clinical trial that—

"(I) is intended to form the primary basis of a claim of effectiveness in support of approval or licensure under section 505 of this Act or section 351 of the Public Health Service Act; and

"(II) is the subject of an active investigational new drug application under section 505(i) of this Act or section 351(a)(3) of the Public Health Service Act, as applicable; and

"(D) the active development or production of which is ongoing and has not been discontinued by the manufacturer or placed on clinical hold under section 505(i); and

"(3) the term 'phase 1 trial' means a phase 1 clinical investigation of a drug as described in section 312.21 of title 21, Code of Federal Regulations (or any successor regulations).

Definition of a 'phase 1 trial'

"(b) EXEMPTIONS.—Eligible investigational drugs provided to eligible patients in compliance with this section are exempt from sections 502(f), 503(b)(4), 505(a), and 505(i) of this Act, section 351(a) of the Public Health Service Act, and parts 50, 56, and 312 of title 21, Code of Federal Regulations (or any successor regulations), provided that the sponsor of such eligible investigational drug or any person who manufactures, distributes, prescribes, dispenses, introduces or delivers for introduction into interstate commerce, or provides to an eligible patient an eligible investigational drug pursuant to this section is in compliance with the applicable requirements set forth in sections 312.6, 312.7, and 312.8(d)(1) of title 21, Code of Federal Regulations (or any successor regulations) that apply to investigational drugs.

"(c) USE OF CLINICAL OUTCOMES.—

"(1) IN GENERAL.—Notwithstanding any other provision of this Act, the Public Health Service Act, or any other provision of Federal law, the Secretary may not use a clinical outcome associated with the use of an eligible investigational drug pursuant to this section to delay or adversely affect the review or approval of such drug under section 505 of this Act or section 351 of the Public Health Service Act unless—

"(A) the Secretary makes a determination, in accordance with paragraph (2), that use of such clinical outcome is critical to determining the safety of the eligible investigational drug; or

Determination.

"(B) the sponsor requests use of such outcomes.

"(2) LIMITATION.—If the Secretary makes a determination under paragraph (1)(A), the Secretary shall provide written notice of such determination to the sponsor, including a public health justification for such determination, and such notice shall be made part of the administrative record. Such determination shall not be delegated below the director of the agency center that is charged with the premarket review of the eligible investigational drug.

Notice. Records.

"(d) REPORTING.—

"(1) IN GENERAL.—The manufacturer or sponsor of an eligible investigational drug shall submit to the Secretary an annual summary of any use of such drug under this section. The summary shall include the number of doses supplied, the

Regulations.

number of patients treated, the uses for which the drug was made available, and any known serious adverse events. The Secretary shall specify by regulation the deadline of submission of such annual summary and may amend section 312.33 of title 21, Code of Federal Regulations (or any successor regulations) to require the submission of such annual summary in conjunction with the annual report for an applicable investigational new drug application for such drug.

"(2) POSTING OF INFORMATION.—The Secretary shall post an annual summary report of the use of this section on the internet website of the Food and Drug Administration, including the number of drugs for which clinical outcomes associated with the use of an eligible investigational drug pursuant to this section was—

"(A) used in accordance with subsection (c)(1)(A);

"(B) used in accordance with subsection (c)(1)(B); and

"(C) not used in the review of an application under section 505 of this Act or section 351 of the Public Health Service Act.".

21 USC 360bbb–0a note.

(b) NO LIABILITY.—

(1) ALLEGED ACTS OR OMISSIONS.—With respect to any alleged act or omission with respect to an eligible investigational drug provided to an eligible patient pursuant to section 561B of the Federal Food, Drug, and Cosmetic Act and in compliance with such section, no liability in a cause of action shall lie against—

(A) a sponsor or manufacturer; or

(B) a prescriber, dispenser, or other individual entity (other than a sponsor or manufacturer), unless the relevant conduct constitutes reckless or willful misconduct, gross negligence, or an intentional tort under any applicable State law.

(2) DETERMINATION NOT TO PROVIDE DRUG.—No liability shall lie against a sponsor manufacturer, prescriber, dispenser or other individual entity for its determination not to provide access to an eligible investigational drug under section 561B of the Federal Food, Drug, and Cosmetic Act.

(3) LIMITATION.—Except as set forth in paragraphs (1) and (2), nothing in this section shall be construed to modify or otherwise affect the right of any person to bring a private action under any State or Federal product liability, tort, consumer protection, or warranty law.

21 USC 360bbb–0a note.

SEC. 3. SENSE OF THE SENATE.

It is the sense of the Senate that section 561B of the Federal Food, Drug, and Cosmetic Act, as added by section 2—

(1) does not establish a new entitlement or modify an existing entitlement, or otherwise establish a positive right to any party or individual;

(2) does not establish any new mandates, directives, or additional regulations;

(3) only expands the scope of individual liberty and agency among patients, in limited circumstances;

(4) is consistent with, and will act as an alternative pathway alongside, existing expanded access policies of the Food and Drug Administration;

(5) will not, and cannot, create a cure or effective therapy where none exists;

(6) recognizes that the eligible terminally ill patient population often consists of those patients with the highest risk of mortality, and use of experimental treatments under the criteria and procedure described in such section 561A involves an informed assumption of risk; and

(7) establishes national standards and rules by which investigational drugs may be provided to terminally ill patients.

Approved May 30, 2018.

LEGISLATIVE HISTORY—S. 204:

CONGRESSIONAL RECORD:
Vol. 163 (2017): Aug. 3, considered and passed Senate.
Vol. 164 (2018): May 22, considered and passed House.
DAILY COMPILATION OF PRESIDENTIAL DOCUMENTS (2018):
May 30, Presidential remarks.

271) 2018-06-28 Zolkefli Y: The ethics of truth-telling in health-care setting. Malays J Med Sci 2018; 25(3): 135-139. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6422557/pdf/14mjms25032018_sc.pdf

272) 2018-07 Clark SA: The impact of the Hippocratic Oath in 2018: The conflict of the ideal of the physician, the knowledgeable humanitarian, versus the corporate medical allegiance to financial models contributes to burnout. Cureus –Open access review article. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6166910/pdf/cureus-0010-00000003076.pdf

273) 2018-July-September Corlett M: Born to Fly. (about Lt. Colonel Thomas Crull) The Novato Historian 2018 July-September; 42 (3): N-9. https://www.novatohistory.org/wp-content/uploads/2018/10/Historian-Vol-42-No3.pdf

274) 2018-07-09 Shepherd B: Trump's two SCOTUS picks also went to high school together. Georgetown Prep could soon control two-ninths of the Supreme Court. https://www.washingtonian.com/2018/07/09/brett-kavanaugh-neil-gorsuch-georgetown-prep/

275) 2018-07-10 Mervosh S: Kavanaugh and Gorsuch both went to the same elite prep school. The New York Times https://www.nytimes.com/2018/07/10/us/kavanaugh-gorsuch-georgetown-prep.html

276) 2018-07-12 FDA: Drug Study Designs—Guidance for Institutional Review Boards and Clinical Investigators, January 1998. Current as of 2018-07-12. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-study-designs

277) 2018-07-18 ACT-IAC (703-208-4800): Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliate Networks (DEAN). https://www.actiac.org/bio/carolyn-clancy-md-macp

278) 2018-08-16 FDA: RADM Denis Hinton, R.N., M.S., Chief Scientist—Office of the Chief Scientist, Biography. https://www.fda.gov/about-fda/fda-organization/denise-hinton#person-bio but a recent update, RADM Hinton served as the FDA Chief Scientist from July 2017 to October 2021 which was throughout the COVID-19 epidemic in the last two years issuing all EUAs regarding COVID-19. RADM Hinton, RN, MS, is now listed as the Deputy U.S. Surgeon General, https://www.usphs.gov/leadership/u-s-surgeon-general/ answering to U.S. Surgeon General, Vice Admiral Vivek H. Murthy https://www.usphs.gov/leadership/u-s-surgeon-general/, 301-496-3432, who answers to the President of the United States of America. (Please note unlike previously, RADM Hinton is no longer listed in the United States Department of Health & Human Services (HHS) Employee Directory, https://directory.psc.gov/employee.htm, attempted to accessed on 12/04/2021).

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279) 2018-08-09 Hawkins WG, Hanto D: Frank Edward Johnson, Jr. M.D. 1943 – 2018, American Surgical Association *Transactions*. https://americansurgical.org/transactions/Fellows/Memoirs/FrankEJohnson.cgi

> Dr. Johnson was born in Evanston, IL, on October 28, 1943 to Frank Edward Johnson, Sr. and Beryl Madeline Johnson. He received his undergraduate and medical degrees from the University of Minnesota in Minneapolis and completed his internship at the University of California Los Angeles. He then traveled around the world for one year prior to serving as a naval doctor during the Vietnam War. He was awarded the Bronze Star Medal for acts of valor and heroism. His time in Vietnam inspired him to work with his dad to create a charitable organization that continues to bring children with cardiac defects from around the world to the US for surgery.

280) 2018-08-09 Saint Louis University obituary: Frank E. Johnson, M.D.: 1943-2018. Frank E. Johnson, M.D., a professor emeritus of surgery at Saint Louis University School of Medicine, died Thursday, Aug. 9. He was 74. https://www.slu.edu/news/2018/august/frank-johnson-obituary.php

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The Dog Lab Chapter 3

With many exotic new methods of conducting medical experiments including genetic testing and high technology in general, there remains a tried and true method of conducting the testing of innovative and potentially life-saving operations and procedures: the "dog lab." For the research physician, physiologist, and surgeon alike, the laboratory specializing in the use of large animals, e.g.: dogs, is the place that physicians are able to test procedures before they are attempted on human beings. Organ transplantation, the development of procedures using endoscopic instruments, the use of lasers to perform surgery on the human eye and even surgery through the use of remote controlled robots all had their beginnings in *The Dog Lab.*

Human nature is not only averse to being exposed to the grittiness of life but it collectively wretches in response to such exposures. As demonstrated by Hurricane Katrina in August of 2005, life's realities are stark, stomach turning and piercing. And yet, much of modern life is littered with a grittiness that we cannot indulge in the focus of the mind's eye. Whether it is the irresolvable nature and sordidness of abortion, the unimaginable, brutal and inhumane nature of the Nazi experiments on human beings or research of the Tuskegee Study of African Americans with syphilis in which penicillin was deliberately withheld in an effort to better understand how the disease is spread and what its effects are on the human body, we have little stomach for such mind numbing sordidness. The slaughtering of animals for their fur and for the protein flesh they provide for our daily fare comes even closer to scarring placid images of the good life as it is lived on a daily basis.

The use of dogs as vehicles for surgeons to learn how to perform new operations strikes a similar chord. It is abrasive to human consciousness to think that dogs are expendable for such purposes, especially since so many fellow citizens treasure them as family members. Dog labs are decades old and by nature experimental. Given their unsung role in the development of American surgical procedures, it is no small wonder that legions of dogs have

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been sacrificed on the altar of learning. As such, dog labs have come to represent a slaughter house of sorts, a place where the life of an animal is put at risk or sacrificed for the good of learning how to do something that would be of benefit to human kind. Due to the bloody and unsavory light in which the dog lab has come to be cast in the minds of surgical medicine, the dog lab has come to represent disparaging metaphor of sometime unconscionable practices.

Many years ago, the term "dog lab" was used as an instructional metaphor to then this newly named Veterans Administration (VA) hospital's Chief of Surgery. A fellow senior surgeon offered the term as a description and an explanation of how some physicians have historically viewed the relationship between VA hospitals in general and the medical schools with which they affiliated over the course of the last sixty years. Thus, historically, the metaphor epitomizes the derogatory sentiments and allusions that some physicians and medical educators have made in the presence of their educational charges regarding the indigent and less-fortunate who are treated in our nation's largest public hospital system.

The callous use of such a demeaning metaphor signals nothing less than a diminishment of human worth. In the verbal attitudes they express, all too often medical educators as role models convey implied values that impart heavy and unfortunately lasting meaning for their students. It is the method by which values both ill and good are transmitted over the course of generations. Even if untrue[1] initially and intended in reference to only one VA hospital, "The Dog Lab" is unimaginably derogatory to the U.S. Department of Veterans Affairs as an institution implying a substandard system of health care. Furthermore, it demeans and condemns those veterans who utilize the VA as their primary source of healthcare as somewhat less-than-human experimental subjects. And yet, it is the country's veterans who exposed themselves in harms' way to protect our way of life throughout our nation's history. It is those same veterans who knowingly served their country not knowing when they were inducted and swore allegiance to the country whether they would be stateside for the duration of their military career or die in combat within six months of their induction. It is those very same veterans to whom Abraham Lincoln 140 years ago promised on our behalf: **"...to care for him who shall have borne the battle, and for his widow, and his orphan..."** It is those veterans--the short, the long and the tall, the drug addicted or alcoholic, homeless, chronically mentally ill and rife with unrelenting PTSD--to whom we owe our way of life. The manner in which they are treated in the healthcare system dedicated to them reflects on the very character of our country.

[1]VA hospitals have been recognized in recent studies as providing an above average standard of healthcare quality. See *U.S. News & World Report*. July 18, 2005

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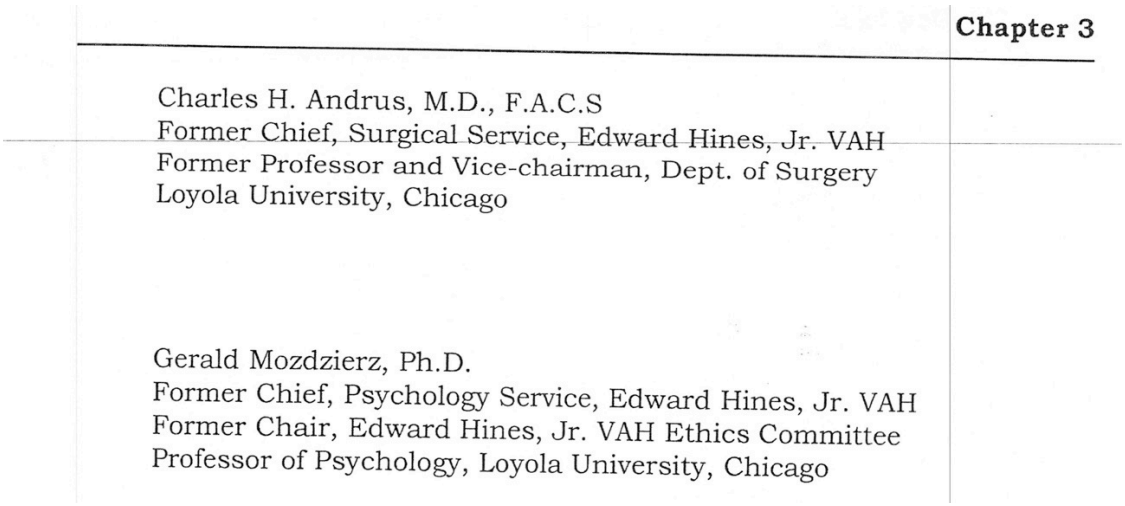

Chapter 3

Charles H. Andrus, M.D., F.A.C.S
Former Chief, Surgical Service, Edward Hines, Jr. VAH
Former Professor and Vice-chairman, Dept. of Surgery
Loyola University, Chicago

Gerald Mozdzierz, Ph.D.
Former Chief, Psychology Service, Edward Hines, Jr. VAH
Former Chair, Edward Hines, Jr. VAH Ethics Committee
Professor of Psychology, Loyola University, Chicago

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How to Lie With Statistics is a 65-year-old book that can be read in an hour and will teach you more practical information you can use every day than any book on "big data" or "deep learning." For all promised by machine learning and petabyte-scale data, the most effective techniques in data science are still small tables, graphs, or even a single number that summarize a situation and help us — or our bosses — make a decision informed by data.

Time and again, I've seen thousands of work hours on complex algorithms summarized in a single number. Ultimately, that's how the biggest decisions are made: with a few pieces of data a human can process. This is why lessons from "How to Lie with Statistics" (by Darell Huff) are relevant even though each of us probably generates more data in a single day than existed in the entire world at the writing of the book. As producers of tables and graphs, we need to effectively present valid summaries. As consumers of information, we need to spot misleading/exaggerated statistics which manipulate us to take action that benefits someone else at our expense.

These skills fall under a category called "data literacy": the ability to read, understand, argue with, and make decisions from information. Compared to algorithms or big data processing, data literacy may not seem exciting, but it should form the basis for any data science education. Fortunately, these core ideas don't change much over time and often the best books on the subject (such as The Visual Display of Quantitative Information) are decades old. The classic book discussed in this article addresses responsible consumption of data in a concise, effective, and enjoyable format. Here are my lessons learned from "How to Lie with Statistics" with commentary from my experiences.

4. Small Samples Produce Shocking Statistics
Would you be surprised if I told you the highest cancer rates tend to occur in the counties with the smallest populations? Not that shocking. How about when I add that the lowest cancer rates also tend to occur in counties with the lowest number of people? This a verified example of what occurs with small sample sizes: extreme values.

Any time researchers conduct a study, they use what is called a sample: a subset of the population meant to represent the entire population. This might work fine when the sample is large enough and has the same distribution of the larger population, but often, because of limited funding or response rates, psychological, behavioral, and medical studies are conducted with small samples, leading to results that are questionable and cannot be reproduced.

Scientists are usually limited to small samples by legitimate problems, but advertisers use small numbers of participants in their favor by conducting many tiny studies, one of which will produce a positive result. Humans are not great at adjusting for sample sizes when evaluating a study which in practice means we treat the results of a 1000 person trial the same as a 10 person trial. **This is known as "insensitivity to sample size" or "sample size neglect".**

8. Look for Bias in Sample Selection
Remember when we talked about all data being gathered from samples which we hope are representative of the population? In addition to being concerned about sample size, we also need to look for any bias in the sample.

This could come from the measurement method used: a landline phone screen might favor wealthier, older participants. It could also come from the physical location: surveying only people who live in cities because it's cheaper might bias results toward more progressive views. Sample bias is particularly prevalent in political polling where 2016 showed that sometimes samples are not representative of an entire population.

When examining a study, we need to ask who is being included in the sample and who is being excluded. For decades, psychology and sociology studies have been hurt by the WEIRD bias. Samples only included

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people (often college students) from Western, Education, Industrialized, Rich, Democratic, Nations. It's hard to reasonably say a survey represents all of humanity when the participants are this limited!

We should also look for sampling bias in our sources of information. Most of us now impose information selection bias on our selves by choosing sources that we tend to agree with. This leads to dangerous situations where we don't encounter people who have different opinions and so we grow more entrenched in our views. The solution to this is simple but difficult: read different sources of news, particularly those that don't agree with you.

If you are a New York Times reader, try the Wall Street Journal for a while. For those who are feeling adventurous, you can even try talking to people who disagree with you. While this may seem intimidating, I've found that people who disagree outwardly often have more in common — the same core driving desires — motivating them to choose their respective sides. It's much easier to come to a common understanding in person but even engaging in civil discourse online is possible and productive and can help you escape a self-imposed information-selection bias.

In summary, we need to be wary both of outside sampling bias and self-created sampling bias from our choice of media sources. You would not like someone telling you to read only a single newspaper, so don't do the same to yourself. Diverse viewpoints lead to better outcomes, and incorporating different sources of information with varying opinions will give you a better overall picture of events. We can't always get to the complete truth of a matter, but we can at least see it from multiple sides. Similarly, when reading a study, make sure you recognize that the sample may not be indicative of the entire population and try to figure out which way the bias goes.

9. Be Wary of "Big Names" on Studies and Scrutinize Authority

Huff describes the idea of an "O.K name" as one added to a study to lend it an air of authority. Medical professionals (doctors), universities, scientific institutions, and large companies have names that lead us to automatically trust the results they produce. However, many times these "experts" did not actually produce the work but only were tangentially involved and the name has been added to sway us. Other times, such as when cigarette makers used doctors to sell their deadly products, the authorities are directly paid to lie. One way to avoid being persuaded by an impressive name is to "make sure the name on the study stands behind the study and not beside it." Don't see an institutional name and immediately assume the study is infallible. I don't think we should look at the author or university until we've analyzed the statistics to avoid any unconscious bias we impose on ourselves.

Even when the results come from a confirmed "expert" that does not mean you should accept them without question. The argument from authority is a fallacy that occurs when we assume someone with greater power is more likely to be correct. This is false because past success has no bearing on whether current results are correct. As Carl Sagan put it: "Authorities must prove their contentions like everybody else." (from *The Demon-Haunted World: Science as a Candle in the Dark*).

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- Serologic response to SARS-CoV-2
  - One study found the serologic response to a recombinant SARS-CoV-2 nucleocapsid: IgM 85.4%, IgA 92.7% (median 5d after the onset of symptoms), and IgG 77.9% (14d after onset).[22]
  - Another study from China using IgM and IgG SARS-CoV-2-specific antibodies found < 40% seropositive if illness less than 7d, rising to ~100% 15d or more after onset.
  - Asymptomatically infected individuals produce antibodies to lesser levels and may fall below levels of detection within 2–3 months.[23]

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Abstract

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Cancer patients who have exhausted standard treatments often seek access to investigational drugs. Often, however, such access is unavailable, due to either the unavailability of a trial, lack of an open recruiting spot on the trial, even when the trial itself is open, or the inability of the patient to meet one or more trial eligibility criteria. In such settings patients often seek access to investigational agents outside of a trial. The federal "Right to Try" legislation was passed to create an additional avenue, different from the FDA's Expanded Access, or "Compassionate Use" Program, through which patients might obtain access to investigational drugs. A year after this legislation was signed into law, there remains both a limited awareness of it and a substantial degree of misunderstanding on the part of those who are aware of it. The law creates an avenue to greatly facilitate off-study administration when patient, physician and the manufacturer are all in agreement regarding the off study use of an eligible investigational agent. The law does not, however, empower a patient to impose a demand on either a provider or a drug manufacturer, nor does it require any entity to provide financial coverage for the drug. Eligible drugs are those which are not approved by the FDA for any indication, have completed a phase I trial, have an ongoing pivotal trial, and have an active registration plan. We review the specific law with commentary on its implications for improved access to investigational drugs outside of clinical trials.

Summary.

RTT creates a pathway for patients to receive an investigational drug outside of a clinical trial if, and only if, the patient is eligible, the drug is eligible, and the patient, drug manufacturer, and treating physician all agree that they wish to pursue this path. This legislation does not empower the patient to compel either a physician or a drug company to provide a drug under this Act. For the patient to be eligible, that patient must have a life- threatening disease or condition, must have exhausted standard care options, and must not have access to the drug on a clinical trial. For the drug to be eligible, it must not be approved by the FDA for any indication, must have completed a phase I trial, and must have an ongoing pivotal trial. The number of times in which all eligibility criteria for the patient and the drug are met, and all parties agree to proceed, will be limited, however, in such scenarios, RTT provides a pathway which is far simpler and requires far less consultation, documentation, and reporting than the FDA's Expanded Access Program, thus facilitating access to eligible investigational agents for eligible patients.

Table 1.

Summary of "Right to Try" Act

Requirements for Patient
- a. Life-threatening condition
- b. Exhausted standard treatment options
- c. Unable to participate in an ongoing trial
- d. Provide informed consent

Requirements for Drug
- a. Phase I trial completed
- b. Ongoing pivotal phase II or III trial
- c. Active development plan to seek FDA approval
- d. Not approved for any indication

Requirement for the Physician
- a. Be in good standing with licensing organization or board
- b. Certify that patient is unable to participate in a clinical trial involving the drug in question
- c. Accept written informed consent from patient or authorized representative.
- d. Receive no compensation from the Sponsor/manufacturer

Requirements for Sponsor/Manufacturer
- a. Comply with standard procedures for investigational drug labeling, promotion,

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and recovery of direct costs.

b. Submit an annual summary of the use of the drug to the FDA, including number of doses supplied, number of patients treated, the uses for which the drug was made available, and any known serious adverse events.

Liabilities and Mandates

a. No liability for a manufacturer's decision not to provide drug
b. No liability for a physician's decision not to prescribe drug
c. No mandate for any entity to provide coverage for drug or associated care
d. No positive right established to any individual

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> **H**uman coronaviruses (HCoVs) have long been considered inconsequential pathogens, causing the "common cold" in otherwise healthy people. However, in the 21st century, 2 highly pathogenic HCoVs—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)—emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality. In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019-nCoV), was recognized in Wuhan, China, and has caused serious illness and death. The ultimate scope and effect of this outbreak is unclear at present as the situation is rapidly evolving.
>
> Coronaviruses are large, enveloped, positive-strand RNA viruses that can be divided into 4 genera: alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans.[1] Four HCoVs (HCoV 229E, NL63, OC43, and HKU1) are endemic globally and account for 10% to 30% of upper respiratory tract infections in adults. Coronaviruses are ecologically diverse with the greatest variety seen in bats, suggesting that they are the reservoirs for many of these viruses.[2] Peridomestic mammals may serve as intermediate hosts, facilitating recombination and mutation events with expansion of genetic diversity. The surface spike (S) glycoprotein is critical for binding of host cell receptors and is believed to represent a key determinant of host range restriction.[1]
>
> Until recently, HCoVs received relatively little attention due to their mild phenotypes in humans. This changed in 2002, when cases of severe atypical pneumonia were described in Guangdong Province, China, causing worldwide concern as disease spread via international travel to more than 2 dozen countries.[2] The new disease became known as severe acute respiratory syndrome (SARS), and a beta-HCoV, named SARS-CoV, was identified as the causative agent. Because early cases shared a history of human-animal contact at live game markets, zoonotic transmission of the virus was strongly suspected.[3] Palm civets and raccoon dogs were initially thought to be the animal reservoir(s); however, as more viral sequence data became available, consensus emerged that bats were the natural hosts.
>
> Common symptoms of SARS included fever, cough, dyspnea, and occasionally watery diarrhea.[2] Of infected patients, 20% to 30% required mechanical ventilation and 10% died, with higher fatality rates in older patients and those with medical comorbidities. Human-to-human transmission was documented,

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mostly in health care settings. This nosocomial spread may be explained by basic virology: the predominant human receptor for the SARS S glycoprotein, human angiotensin-converting enzyme 2 (ACE2), is found primarily in the lower respiratory tract, rather than in the upper airway. Receptor distribution may account for both the dearth of upper respiratory tract symptoms and the finding that peak viral shedding occurred late (≈10 days) in illness when individuals were already hospitalized. SARS care often necessitated aerosol-generating procedures such as intubation, which also may have contributed to the prominent nosocomial spread.

Several important transmission events did occur in the community, such as the well-characterized mini-outbreak in the Hotel Metropole in Hong Kong from where infected patrons traveled and spread SARS internationally. Another outbreak occurred at the Amoy Gardens housing complex where more than 300 residents were infected, providing evidence that airborne transmission of SARS-CoV can sometimes occur.[4] Nearly 20 years later, the factors associated with transmission of SARS-CoV, ranging from self-limited animal-to-human transmission to human superspreader events, remain poorly understood.

Ultimately, classic public health measures brought the SARS pandemic to an end, but not before 8098 individuals were infected and 774 died.[2] The pandemic cost the global economy an estimated $30 billion to $100 billion.[1] SARS-CoV demonstrated that animal CoVs could jump the species barrier, thereby expanding perception of pandemic threats.

In 2012, another highly pathogenic beta-CoV made the species jump when Middle East respiratory syndrome (MERS) was recognized and MERS-CoV was identified in the sputum of a Saudi man who died from respiratory failure.[3] Unlike SARS-CoV, which rapidly spread across the globe and was contained and eliminated in relatively short order, MERS has smoldered, characterized by sporadic zoonotic transmission and limited chains of human spread. MERS-CoV has not yet sustained community spread; instead, it has caused explosive nosocomial transmission events, in some cases linked to a single superspreader, which are devastating for health care systems. According to the World Health Organization (WHO), as of November 2019, MERS-CoV has caused a total of 2494 cases and 858 deaths, the majority in Saudi Arabia. The natural reservoir of MERS-CoV is presumed to be bats, yet human transmission events have primarily been attributed to an intermediate host, the dromedary camel.

MERS shares many clinical features with SARS such as severe atypical pneumonia, yet key differences are evident. Patients with MERS have prominent gastrointestinal symptoms and often acute kidney failure, likely explained by the binding of the MERS-CoV S glycoprotein to dipeptidyl peptidase 4 (DPP4), which is present in the lower airway as well as the gastrointestinal tract and kidney.[3] MERS necessitates mechanical ventilation in 50% to 89% of patients and has a case fatality rate of 36%.[2]

While MERS has not caused the international panic seen with SARS, the emergence of this second, highly pathogenic zoonotic HCoV illustrates the threat posed by this viral family. In 2017, the WHO placed SARS-CoV and MERS-CoV on its Priority Pathogen list, hoping to galvanize research and the development of countermeasures against CoVs.

The action of the WHO proved prescient. On December 31, 2019, Chinese authorities reported a cluster of pneumonia cases in Wuhan, China, most of which included patients who reported exposure to a large seafood market selling many species of live animals. Emergence of another pathogenic zoonotic HCoV was suspected, and by January 10, 2020, researchers from the Shanghai Public Health Clinical Center & School of Public Health and their collaborators released a full genomic sequence of 2019-nCoV to public databases, exemplifying prompt data sharing in outbreak response. Preliminary analyses indicate that 2019-nCoV has some amino acid homology to SARS-CoV and may be able to use ACE2 as a receptor. This has important implications for predicting pandemic potential moving forward. The situation with 2019-nCoV is

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evolving rapidly, with the case count currently growing into the hundreds. Human-to-human transmission of 2019-nCoV occurs, as evidenced by the infection of 15 health care practitioners in a Wuhan hospital. The extent, if any, to which such transmission might lead to a sustained epidemic remains an open and critical question. So far, it appears that the fatality rate of 2019-nCoV is lower than that of SARS-CoV and MERS-CoV; however, the ultimate scope and effects of the outbreak remain to be seen.

Drawing on experience from prior zoonotic CoV outbreaks, public health authorities have initiated preparedness and response activities. Wuhan leaders closed and disinfected the first identified market. The United States and several other countries have initiated entry screening of passengers from Wuhan at major ports of entry. Health practitioners in other Chinese cities, Thailand, Japan, and South Korea promptly identified travel-related cases, isolating individuals for further care. The first travel-related case in the United States occurred on January 21 in a young Chinese man who had visited Wuhan.

Additionally, biomedical researchers are initiating countermeasure development for 2019-nCoV using SARS-CoV and MERS-CoV as prototypes. For example, platform diagnostic modalities are being rapidly adapted to include 2019-nCoV, allowing early recognition and isolation of cases. Broad-spectrum antivirals, such as remdesivir, an RNA polymerase inhibitor, as well as lopinavir/ritonavir and interferon beta have shown promise against MERS-CoV in animal models and are being assessed for activity against 2019-nCoV.[5] Vaccines, which have adapted approaches used for SARS-CoV or MERS-CoV, are also being pursued. For example, scientists at the National Institute of Allergy and Infectious Diseases Vaccine Research Center have used nucleic acid vaccine platform approaches.[6] During SARS, researchers moved from obtaining the genomic sequence of SARS-CoV to a phase 1 clinical trial of a DNA vaccine in 20 months and have since compressed that timeline to 3.25 months for other viral diseases. For 2019-nCoV, they hope to move even faster, using messenger RNA (mRNA) vaccine technology. Other researchers are similarly poised to construct viral vectors and subunit vaccines.

While the trajectory of this outbreak is impossible to predict, effective response requires prompt action from the standpoint of classic public health strategies to the timely development and implementation of effective countermeasures. The emergence of yet another outbreak of human disease caused by a pathogen from a viral family formerly thought to be relatively benign underscores the perpetual challenge of emerging infectious diseases and the importance of sustained preparedness.

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Article Information

Corresponding Author: Anthony S. Fauci, MD, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, 31 Center Dr, MSC 2520, Bldg 31, Room 7A-03, Bethesda, MD 20892-2520 (afauci@niaid.nih.gov).

Published Online: January 23, 2020. doi:10.1001/jama.2020.0757

Conflict of Interest Disclosures: None reported.

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> DR. SCHLEIFER: Thanks, Mr. President, for having us. I'm Lenny Schleifer, the founder and CEO of Regeneron, a company that I built with George Yancopoulos over the last 30 years. And we are a monoclonal antibody primarily centered company. We are no strangers to collaborating with the administration. We work with Secretary Azar's group, BARDA. And we came up with a cure for Ebola, and we're very proud of that. Dr. Fauci's group was really instrumental in testing that under unbelievable conditions in the Congo. And it didn't create quite as much excitement, because, thank goodness, it didn't hit our shores.

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But we can use the exact same technology, and we already have. We have 1,000 antibodies that are already sitting in dishes. We're screening them. We're selecting them. We anticipate, if all goes well, 200,000 doses per month can come out of our factory in New York, starting in August.

The unique thing about our technology —

THE PRESIDENT: That means you'd be able to use the vaccine that early?

DR. SCHLEIFER: It depends on what we see; how we work closely with the FDA, which we will do. The FDA already reached out to us, but we've got to work closely.

THE PRESIDENT: So that process would be faster than John's?

DR. SCHLEIFER: It would be. The —

SECRETARY AZAR: Can you explain why that would be?

DR. SCHLEIFER: Well, so, we make passive vac- — vaccine and therapeutic — therapeutic. Our drug will be able to protect you. Whether or not you're infected, it'll protect you from getting infected. Or if you are infected, it would treat you. And the — we have just taken processes that normally take years — literally, years — and we put them end-to-end and now do them in weeks to months, which nobody else in the industry can do.

So we're very excited to collaborate once again.

THE PRESIDENT: So this would be a combination of a vaccine and also it will — to put it in a different way — make you better, quicker.

DR. SCHLEIFER: Yeah. Well, think of it this way: If you — if you get immunized with one of these vaccines, you're going to make some antibodies to protect you. We're going to already make those antibodies and give them to you so you don't have to go through that whole process. So it'll protect you.

And, as we showed with Ebola, if you give enough of them — we — it was lifesaving, life- — truly lifesaving.

THE PRESIDENT: That's true.

DR. SCHLEIFER: And it beat out the antivirals. It really — it was the way to go. It's very predictable.

I just want to say, I hope everybody succeeds here. I mean, this is — bringing everybody together here is really critical and there's going to be success. This industry is really talented, as an industry. Sometimes we run astray, but we're going to get this done.

THE PRESIDENT: Thank you very much. Thanks, Len. Appreciate it. Please.

333) 2020-03-02 Einenkel W: Watch Trump's complete lack of scientific knowledge on full display in coronavirus meeting (/stories/2020/3/2/1923639/ -Watch-Trump-s-complete-lack-of-scientific-knowledge-on-full-dispay-in-coronavirus-meeting). https://www.dailykos.com/stories/2020/3/2/1923639/-Watch-Trump-s-complete-lack-of-scientific-knowledge-on-full-display-in-coronavirus-meeting

> *Dr. Leonard Schleifer, Regeneron Pharmaceuticals CEO, explains that, no, vaccines are vaccines and drugs are drugs. Dr. Schleifer: Well, think of it this way, if you get immunized with one of these vaccines, you're going to make antibodies to protect you. We are going to give you those antibodies so you don't have to go through that process.*

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334) 2020-03-02 Facher L: Trump's tone toward pharma shifts, as he looks to drug makers to help with coronavirus response. StatNews. https://www.statnews.com/2020/03/02/trumps-tone-toward-pharma-shifts-coronavirus/

WASHINGTON — President Trump had billed the meeting with pharmaceutical executives as a scolding waiting to happen. The gathering was intended to pressure the industry to bring drug prices "way down," he said on Friday, suggesting it had only later morphed into a "convenient" opportunity to discuss the development of a coronavirus vaccine.

But seated across from 10 pharmaceutical executives in the Cabinet Room on Monday, Trump's long-simmering contempt for the drug industry melted away. Trump told executives from Gilead, Johnson & Johnson, and Pfizer that they worked for a "great company." He affectionately referred to Leonard Schleifer, the CEO of Regeneron, as "Lenny." At one point, Trump referred to the assembled drug executives as "geniuses."

The meeting signified a remarkable shift in Trump's view of the pharmaceutical industry. After years of maintaining that drug companies charge "ripoff" prices, Trump appeared floored by the executives' progress reports. He alternatingly praised CEOs and egged them on to lay out shorter and shorter timelines for bringing a vaccine to market. Trump, throughout the meeting, appeared so blown away by the drug companies' claims that his deputies struggled to rein in his expectations.

"Like I've been telling you, Mr. President," Tony Fauci, the director of the National Institute on Allergy and Infectious Disease, interjected at one point. "A year to a year and a half," he said, referring to the amount of time it will likely take to deploy an effective vaccine to large populations.

Undeterred, Trump continued to ask various versions of the same question: "So what do you think in terms of timing?"

The executives largely told the president what he wanted to hear — that for both therapies and vaccines, companies could enter early testing within months, with the aim of reaching the market in time for peak season in a year's time.

"It was: Tell us how fast you can go, but let's keep safety in mind, and let's make sure we create something manufacturable," said Dan Menichella, CEO of CureVac, who was among the executives seated before Trump. The company, headquartered in Germany and Boston, uses messenger RNA to produce protective antibodies inside patients' bodies, thereby preventing infection. CureVac expects to start testing its coronavirus vaccine in healthy volunteers by June, with further trials to come if the injection proves safe.

But even as Fauci and health secretary Alex Azar interrupted to caution the president that most therapies and vaccines were nowhere near ready, the president leaned into the executives' positive spin.

"That's very exciting," Trump said at one point to Daniel O'Day, the CEO of the biotech giant Gilead Sciences, after he described progress on a therapy that could be used to mitigate coronavirus symptoms. "Get it done, Daniel. Don't disappoint us."

Fueling Trump's optimism: When questioned by the president, drug company representatives often struggled to differentiate between projections for bringing drugs to late-stage trials and bringing them to market — so much so that Fauci became a de facto referee.

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At one point, he responded to Stephane Bancel, the chief executive officer of Moderna, with a stern clarification: "You won't have a vaccine — you'll have a vaccine to go into testing."

But he immediately pivoted to Regeneron's Schleifer.

"But Lenny is talking about two months," Trump replied. "I mean, I like the sound of a couple of months better."

335) 2020-03-03 pharmaphorum: CEOs give Trump 'Biology 101' lesson as coronavirus causes election nerves. https://pharmaphorum.com/news/ceos-give-trump-biology-101-lesson-as-coronavirus-causes-election-nerves/

i. The meeting turned into a kind of Biology 101 lesson for a perplexed-looking Trump from the likes of GlaxoSmithKline's CEO Emma Walmsley, Gilead's CEO Daniel O'Day, Johnson & Johnson's chief scientific officer Paul Stoffels, and Regeneron's CEO Leonard Schleifer.
ii. Health secretary Alex Azar kicked off the meeting by asking the pharma execs to find ways to hasten development of a vaccine.
iii. And there was a sense of tension in the room as it became apparent that it's unlikely one will be approved and ready to use ahead of the presidential elections in November.
iv. In a progress briefing from Schleifer, Trump praised Regeneron for its progress so far before asking whether a flu vaccine would work against COVID-19.
v. Trump said: "You take a solid flu vaccine – you don't think that would have an impact or much of an impact on corona?"
vi. The answer from Schleifer was a flat "no", with Anthony Fauci from the National Institutes for Healthcare softening the blow with "probably not".
vii. Trump asked Gilead's O'Day to hurry trials of its antiviral drug remdesivir begun this week, telling the CEO to "get it done".
viii. He added: "Don't disappoint us, Daniel. Do you understand? Great company. Really great."
ix. Trump also quizzed J&J's Stoffels about the timeline for the development of that company's vaccine and noted that the US pharma's vaccine will not be ready until next season.
x. Azar went on to lay out a time frame for development of various therapeutic options for the president, noting that antivirals will likely be ready first, ahead of monoclonal antibodies from Regeneron, followed by vaccines.
xi. Summarising, Trump said: "I will tell you, the whole thing with therapeutics, to me, is very exciting. And, obviously, vaccines. But therapeutics is very exciting, especially when you're so far advanced. That's great. That's really great. Thank you."

336) 2020-03-05. YouTube: Regeneron's Leonard S. Schleifer meets with Trump at the White House, 3/2/2020. https://www.youtube.com/watch?v=31i6p_stzW8 AT THIS MEETING, PRESIDENT TRUMP AND ALL THE PEOPLE OF THE WORLD WERE MISLED BY OMISSION / MISREPRESENTING THE DISTINCTION BETWEEN *ACTIVE IMMUNIZATION (vaccines)* versus *PASSIVE IMMUNIZATION (convalescent plasma, convalescent sera, monoclonal antibodies, monoclonal antibody cocktail, etc.)*. The cost of production of a dose (1/2 unit of fresh frozen plasma) COVID-19 Convalescent Plasma (CCP) which was available in March 2020 is ~$200 while a dose of

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REGEN-COV™ (Casirivimab with imdevimab) which would be several months into the future and would cost ~$3000 a dose. A monoclonal antibody is specific for one antigen (e.g. a specific site on the spike point) and is likely to be ineffective on future variants like Omicron. Polyclonal antibodies like Convalescent Plasma will have multiple antibodies of such sites as on the spike protein and will be available as the SARS-CoV-2 mutates. (e.g. more effective on the Omicron variant).

******* Full 56:54 minute meeting in *The White House* where they went around the table introducing the key players: https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus with the complete transcript: https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/** This **linchpin** *White House* meeting included CEOs, presidents, and Medical Directors of the major biomedical and pharmaceutical companies who could provide vaccines, monoclonal antibodies, and antivirals; the Secretary of the U.S. Department of Health and Human Services and its agencies (e.g.: FDA, NIH, CDC, etc.); and the Vice-president and the President of the United States of American. 1.) Nobody defined the foundational basics of Clinical Immunology: Active Immunization and Passive Immunization. 2.) Everything was in Generalities – NOT THE INDIVIDUAL PATIENT! 3.) The not-for-profit American Red Cross was *NOT* officially invited "to the table" until July 30, 2020—by that time, the U.S.A. had gone so far down the Rabbit Hole, they did not know how to get out! 4.) No physician in that room, on that day, has probably cared for the individual patient since Medical School.

Individuals at the White House meeting of March 2, 2020.

President Donald Trump, 2 years Fordham University and the 2 years Wharton School of the University of Pennsylvania, B.S. in Economics

Alexander Azar, Secretary of the U.S. Department of Health and Human Services, summa cum laude in government and economics from Dartmouth and J.D. from Yale University

Emma Walmsley , CEO of GlaxoSmithKline, MA in Classics and Modern Languages from Oxford University (Christ Church)

Anthony Fauci, M.D., Director of the NIAID of the NIH, College of the Holy Cross with a BA in classics and a MD from Cornell University graduating 1st in his class

Robert Redfield, M.D., Director of the CDC, graduated from Georgetown University's College of Arts and Sciences with a BS and MD from Georgetown University School of Medicine

Daniel Menichella, CEO of CureVac, BA in economics from Harvard University and a MBA from University of North Carolina at Chapel Hill

John Shiver,PhD, Senior Vice President, Vaccines Global R&D at Sanofi Vaccines, BS in Chemistry/Mathematics, Woffard College and a PhD in Chemistry from the University of Florida

Leonard Schleifer, M.D., PhD, CEO Regeneron, BS at Cornell University and an MD-PhD from the University of Virginia

Stephane Bancel, CEO of Moderna, masters degrees from both CentraleSupélec of Paris-Saclay University (engineering) and the University of Minnesota (biological engineering) and an MBA from Harvard Business School

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Daniel O'Day, BS, MBA, Chairman and CEO of Gilead Sciences has a BS in biology from Georgetown University and an MBA from Columbia University in New York

Steven Hahn, M.D., Commissioner, U.S. Food and Drug Administration, BA in Biology from Rice University and MD from Temple University

Mikael Dolsten, M.D., Ph.D., Chief Scientific Officer of Pfizer, Ph.D. in tumor immunology and a MD from Lund University

Joseph Kim, Ph.D., Inovio Pharmaceuticals, BS degrees in Chemical Engineering and Economics from MIT, a Ph.D. in immunology from the University of Pennsylvania, and an MBA in finance from the Wharton School of Business, University of Pennsylvania

Paul Stoffels, M.D., Chief Scientific Officer of Johnson & Johnson, studied medicine at the University of Diepenbeek and the University of Antwerp in Belgium and Infectious Diseases and Tropical Medicine at the Institute of Tropical Medicine in Antwerp, Belgium.

Anne Schuchat, M.D., Principal Deputy Director of the CDC, Swarthmore College and MD Dartmouth Medical School

Stanley Erck, President and CEO of Novavax, undergraduate degree from the University of Illinois and MBA in economics and finance from the Booth School of Business, The University of Chicago

Ambassador Deborah Birx, M.D., U.S. Department of State, BS in chemistry from Houghton College and MD from Pennsylvania State University.

337) 2020-03-05 Herper M, Feuerstein A: How blood plasma from recovered patients could help treat the new coronavirus. STATnews Mar 5, 2020, 1-7. https://www.statnews.com/2020/03/05/how-blood-plasma-from-recovered-patients-could-help-treat-coronavirus/

338) 2020-03-09 Johns Hopkins University & Medicine Coronavirus Resource Center: First date documented by the Internet Archive (Wayback Machine: https://archive.org/web/) to have been published. https://coronavirus.jhu.edu/map.html

339) 2020-03-09 U.S. Department of Health & Human Services, Centers for Medicare and Medicaid Services: Center for clinical standards and quality/quality, safety and oversight group. Ref: QSO-20-15 Hospital/CAH/EMTALA https://www.cms.gov/files/document/qso-20-15-hospitalcahemtala.pdf

340) 2020-03-11 Downs Burger J: Novel coronavirus: EMTALA compliance for hospitals with dedicated emergency departments. Arnall, Golden, Gregory LLP https://www.agg.com/news-insights/publications/novel-coronavirus-emtala-compliance-for-hospitals-with-dedicated-emergency-departments-2/

On March 9, 2020, CMS issued a memorandum to State Survey Agency Directors regarding the implications of COVID-19 on providers' EMTALA obligations. In addition to confirming the

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recommendations in our March 6 Client Alert below, the CMS memorandum provides further guidance that hospitals with dedicated emergency departments should review. We highlight a few notable items below.

Hospital Signage: CMS emphasized that it is a violation of EMTALA for hospitals to use signage that presents barriers to individuals who are suspected of having COVID-19 from coming to the emergency room. However, use of signage designed to help direct individuals to various locations on the hospital property for their Medical Screening Exam – such as an alternative screening location – would be acceptable.

What if an individual who meets the screening criteria for suspected COVID-19 wants to leave the hospital against medical advice? Hospitals cannot prevent the individual from leaving against medical advice. However, State or local public health authorities may have such authority under State or local law. Hospitals should coordinate with their local authorities on the appropriate way to handle such situations.

How will CMS handle complaints about violations of EMTALA in connection with individuals presenting with symptoms of COVID-19? CMS states that it will consider the following (along with other factors) when making a determination of whether violations of EMTALA have occurred:

- The individual's clinical condition at the time of presentation to the referring hospital and at the time of the transfer request;
- The capabilities of the referring hospital;
- The screening and treatment activities performed by the referring hospital for the individual;
- Whether the request for transfer was consistent with any nationally recognized guidelines in effect at the time of the transfer request for COVID-19 screening, assessment, including guidance about transfer for further assessment or treatment of suspected or confirmed COVID-19; and
- The capabilities of the recipient hospital and the recipient hospital's capacity at the time of the transfer request.

What will CMS do if a hospital is not following nationally recognized guidelines regarding COVID-19 infection control processes? While EMTALA does not establish requirements for infection control practices, hospitals are expected to adhere to accepted standards of infection control practice and as part of the conditions of participation for Federal health care programs. CMS cautions that hospitals may be cited for deficiencies related to failure to follow accepted infection prevention and control standards of practice. As such, CMS strongly urges hospitals to follow CDC guidance related to COVID-19 infection control procedures. Hospitals should regularly check the official CDC website and consider signing up for the newsletter to receive weekly emails about COVID-19

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Novel coronavirus ("2019-nCoV", also known as "SARS-CoV-2") and the disease it causes – "coronavirus disease 2019" (abbreviated as "COVID-19") has garnered significant public attention since being declared a Public Health Emergency of International Concern by the World Health Organization, and a public health emergency in the United States by the Department of Health and Human Services ("HHS"). Of particular significance to healthcare providers' compliance efforts is whether the President's observation and monitoring of the situation will culminate in a declaration by the President of a national emergency in connection with the incidences of novel coronavirus.

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In the event of a declaration of a national emergency by the President, the requirements of the Emergency Medical Treatment and Labor Act ("EMTALA") may be formally suspended. However, in the absence of such a declaration by the President and a formal suspension of EMTALA, hospitals are required to comply with EMTALA provisions and may be sanctioned for non-compliance. The Centers for Medicare and Medicaid Services ("CMS") has made recommendations regarding the ways in which hospital emergency departments may take adequate precautions in circumstances like these, while also complying with EMTALA mandates in the absence of a formal suspension. We outline these frameworks in further detail below.

What is EMTALA?

EMTALA is a federal law that requires all Medicare-participating hospitals with a dedicated emergency department to take certain actions when any individual comes to the emergency department and requests an examination or treatment of a medical condition, or when such a request is made on the individual's behalf, regardless of the individual's ability to pay. EMTALA was enacted to prevent hospitals from "dumping" patients because the patients could not pay for treatment, or because of other discriminatory purposes. If a hospital is subject to EMTALA, then it must perform an appropriate medical screening exam ("MSE") on the individual to determine if an emergency medical condition ("EMC") exists. The content of the MSE may vary based on the individual's presenting signs and symptoms, so long as the MSE is sufficient to rule out that an EMC exists. The MSE must be performed by qualified personnel, including a physician, physician assistant, nurse practitioner, or registered nurse who is trained to perform MSEs and who is acting within their state's scope of practice. If an EMC does exist, then the hospital must treat and stabilize the EMC within its capabilities to do so, or alternatively, transfer the individual to a hospital that has the capability and capacity to stabilize the EMC. If an EMC does not exist, then the hospital's obligations with regard to EMTALA end.

When Are a Hospital's EMTALA Obligations Suspended During a National Emergency?

It seems to be a common misconception that when a state's governor has declared a state of emergency in response to a disease outbreak (whether COVID-19, the flu, or otherwise), a hospital's MSE and stabilization obligations under EMTALA have been suspended. However, in such situations, a well-meaning hospital can find itself in violation of EMTALA.

In order for a hospital's MSE and stabilization obligations to be suspended, the federal government must first take four formal actions under Section 1135 of the Social Security Act ("Section 1135"):

1. The President, and not the state's governor, must have declared an emergency or a disaster under either the Stafford Act or the National Emergencies Act;
2. The Secretary of Health and Human Services (the "Secretary") must have declared a public health emergency;
3. The Secretary must have invoked his or her waiver authority, which includes giving Congress 48 hours' advance notice; and
4. The Secretary must issue a waiver that would cover the hospital and includes a specific waiver of the EMTALA requirements.

Then, the hospital's state must have formally activated its emergency or pandemic preparedness plan and any redirection or transfer of individuals must be consistent with this plan. Additionally, the EMTALA waiver will not apply to a hospital that has not activated its own disaster protocol.

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When such a waiver is issued, CMS is to provide notice to covered hospitals through its Regional Offices or State Survey Agencies. When an EMTALA waiver is issued for a public health emergency caused by a pandemic infectious disease, such as novel coronavirus, the EMTALA waiver remains in place until the Secretary terminates the declaration of the public health emergency.

What Obligations under EMTALA May be Suspended by a Waiver?

As alluded to above, Section 1135 allows the Secretary to waive the sanctions associated with a hospital for redirecting an individual to an alternative location for the MSE pursuant to a state emergency or pandemic preparedness plan that would otherwise not be allowed under EMTALA. The Secretary may also waive sanctions for a hospital's inappropriate transfer if the transfer was necessitated by the circumstances of the declared emergency. This typically allows a hospital to avoid sanctions when it transfers a patient before the EMC is stabilized. However, a hospital may not discriminate among individuals based on their ability to pay or their payor source while under a waiver. Sanctions for all other EMTALA requirements may not be waived. It is also important to note that a Section 1135 waiver does not, in and of itself, relieve the hospital from any obligations under state or local laws. Note that if a waiver is issued, it only waives the sanctions applicable to the hospital under EMTALA. Therefore, if an individual is harmed by a hospital's negligent transfer or redirection performed under a waiver, then the hospital may be liable to the individual for that harm.

Can a Hospital Request a Waiver if One Has Not Been Issued?

Yes. If an EMTALA waiver has not yet been issued that covers a hospital, then the hospital may request a waiver under Section 1135. Before CMS will consider a waiver request, the federal government must have performed the first three formal actions outlined above. Furthermore, the Secretary must have delegated his or her decision-making regarding EMTALA to CMS. The hospital, or the hospital's representative, typically makes the waiver request to the CMS Regional Office for the region in which the hospital is located.

What are a Hospital's Options if a Waiver is Not Granted?

If a waiver is not granted, hospitals have a couple of options to separate patients presenting with symptoms of COVID-19 in the emergency department, while continuing to meet EMTALA mandates.

Option 1: Set Up On-Campus Alternative Screening Sites. A hospital is not required to perform the MSE within the emergency department itself. A hospital could instead set up alternative sites on its campus to perform certain MSEs. The patient would need to be logged into the emergency department before being redirected to the alternative site, but this process could take place outside of the entrance to the emergency department. CMS recommends that if a hospital implements such a process, then the persons redirecting patients to the alternative site should be qualified to recognize patients who are obviously in need of emergency treatment (for example, a registered nurse). The MSEs performed at the alternative site must meet all the requirements for MSEs required by law.

Option 2: Set Up Off-Campus Alternative Screening Sites. A hospital may set up a screening site that is not on its campus, as long as the location remains under the hospital's control. This arrangement makes compliance with EMTALA somewhat riskier than the first option. The hospital could not, for instance, redirect individuals who have already come to the emergency department to the off-campus location. The hospital could prospectively encourage the general public to go to the off-campus location for screenings related to COVID-19 and/or influenza, and could publically hold out that the location serves a screening center for that specific purpose. In doing so, however, the hospital could not hold the location out as a place that provides care or screening for EMCs in general on an urgent, unscheduled basis. As long as the off-

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campus site is not itself a dedicated emergency department, then EMTALA does not apply to the visit. Significantly, the site should still be staffed by medical personnel qualified to evaluate individuals presenting with symptoms of COVID-19 and/or flu-like symptoms.

Conclusion

Certain EMTALA obligations may be waived during a national emergency when the federal government takes formal actions specified in the Social Security Act. This waiver only applies to hospitals that (1) are located in states that have formally activated their emergency or pandemic preparedness plan and (2) have activated their own disaster protocol. Even under a waiver, hospitals must continue to meet all non-waived EMTALA obligations. If a waiver has not been issued, then a hospital may apply to CMS for a waiver. If a waiver is not granted, then the hospital may redirect individuals to an alternative screening site located on the hospital's campus so long as all EMTALA requirements are met. A hospital may also set up alternative screening sites off of its campus; however, patients who have already presented to the emergency department may not be redirected to these sites.

If you have any questions about whether your emergency department's operational plan or disaster protocol is compliant with EMTALA or would like assistance requesting a Section 1135 waiver, please contact Jennifer Burgar, Ryan Kerr or Nirouz Elhammali.

Summary and Practical Tips for EMTALA Compliance

- The federal government can waive certain EMTALA requirements during a declared public health emergency.
- Federal and state governments and the hospital must take specific formal actions before these requirements are waived.
- The Secretary of HHS may only waive the sanctions associated with redirecting individuals for their medical screening exam and for transfer that would otherwise be inappropriate under EMTALA.
- If an individual is redirected for a medical screening exam or is inappropriately transferred under a waiver, then the redirection or transfer must not have been made for a discriminatory purpose.
- A hospital must continue to meet all other EMTALA obligations.
- The hospital remains liable in legal actions by individuals who are harmed by redirection or transfers made under a waiver.
- A hospital can request a waiver from CMS if one has not been granted.
- Without a waiver, a hospital may redirect patients for a COVID-19 or other influenza-like illness screening to an alternative on-campus location so long as the hospital's EMTALA obligations continue to be met
- Without a waiver, a hospital may make off-campus locations available for such illness screenings so long as the location is under the control of the hospital and individuals who come to the emergency department are not redirected to these locations.

341) 2020-03-13 Casadevall A, Pirofski L: The convalescent sera option for containing COVID-19. [jci.org, Journal of Clinical Investigation 130 (4); April 2020: 1545-1548]. https://www.jci.org/articles/view/138003. https://www.jci.org/articles/view/138003/pdf

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A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutrallizing the initial inoculum, which is likely to be much smaller than that of established disease (5). Another explanation is that antibody works by modifying the inflammatory response, which is also more easily achieved during the initial immune response, which is also more easily achieved during the initial immune response, a stage that may be asymptomatic (6). …

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues, and provide protective against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months…..

Figure 1. Schematic of the use of convalescent sera for COVID-19. *An individual who is sick with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infections in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than the treatment of established disease.*

342) 2020-03-13 Hixenbaugh M: Doctors push for treatment of coronavirus with blood from recovered patients. NBC News, March 12, 2020. https://www.nbcnews.com/health/health-care/doctors-push-treatment-coronavirus-blood-recovered-patients-n1158476

When Casadevall learned in December that a new coronavirus was spreading rapidly in China, he stared telling colleagues that it might be time to revive the antiquate treatment.

"I'm an infectious disease doctor who is interested in history," Casadevall said. "I knew the history of what was done in the early 20th century with epidemics. The didn't have vacccines then, they didn't have any drugs then – just like the situation we face now. But physicians then knew that , for certain conditions, you could take the blood of the immune and use it to prevent disease or treat those who became ill."

In a paper published Friday in the Journal of Clinical Investigation, Casadevall and a colleague, Dr. Liise-anne Pirofski argued that collecting blood serum or plasma from previously infected people might be the best hope for treating severe cases of COVID-19, the disease caused by the virus, at least until a better treatment can be developed.

343) 2020-03-13 Trump DJ: Proclamation on declaring a national emergency concerning the novel coronavirus disease (COVID-19) outbreak. The White House. https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/

Section 1. Emergency Authority. The Secretary of HHS may exercise the authority under section 1135 of the SSA to temporarily waive or modify certain requirements of the Medicare, Medicaid, and State Children's Health Insurance programs and of the Health Insurance Portability and

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Accountability Act Privacy Rule throughout the duration of the public health emergency declared in response to the COVID-19 outbreak.

344) 2020-03-13 Azar AM: Waiver or modification of requirements under section 1135 of the Social Security Act. www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx *de facto*, I allege that the interpretation of this document became the justification of abridgement of individual American rights to *Passive Immunization* and the antiviral drug Remdesivir, guaranteed under EMTALA (the Emergency Medical Treatment and Labor Act of COBRA, Consolidated Omnibus Budget Act of 1986, PL-99-272), and the Right to Tray Act of 2018, PL-115-176. Copied verbatim:

Waiver or Modification of Requirements Under Section 1135 of the Social Security Act

March 13, 2020

1. Pursuant to Section 1135(b) of the Social Security Act (the Act) (42 U.S.C. § 1320b-5), I, Alex M. Azar II, Secretary of Health and Human Services, hereby waive or modify the following requirements of titles XVIII, XIX, and XXI of the Act and regulations thereunder, and the following requirements of Title XI of the Act, and regulations thereunder, insofar as they relate to Titles XVIII, XIX, and XXI of the Act, but in each case, only to the extent necessary, as determined by the Centers for Medicare & Medicaid Services, to ensure that sufficient health care items and services are available to meet the needs of individuals enrolled in the Medicare, Medicaid and CHIP programs and to ensure that health care providers that furnish such items and services in good faith, but are unable to comply with one or more of these requirements as a result of the consequences of the 2019 Novel Coronavirus (previously referred to as 2019-nCoV, now as COVID-19) pandemic, may be reimbursed for such items and services and exempted from sanctions for such noncompliance, absent any determination of fraud or abuse:

   a. Certain conditions of participation, certification requirements, program participation or similar requirements for individual health care providers or types of health care providers, including as applicable, a hospital or other provider of services, a physician or other health care practitioner or professional, a health care facility, or a supplier of health care items or services, and pre-approval requirements.

   b. Requirements that physicians or other health care professionals hold licenses in the State in which they provide services, if they have an equivalent license from another State (and are not affirmatively barred from practice in that State or any State a part of which is included in the emergency area).

   c. Sanctions under section 1867 of the Act (the Emergency Medical Treatment and Labor Act, or EMTALA) for the direction or relocation of an individual to another location to receive medical screening pursuant to an appropriate state emergency preparedness plan or for the transfer of an individual who has not been stabilized if the transfer is necessitated by the circumstances of the declared Federal public health emergency for the COVID-19 pandemic.

   d. Sanctions under section 1877(g) (relating to limitations on physician referral) under such conditions and in such circumstances as the Centers for Medicare & Medicaid Services determines appropriate.

   e. Limitations on payments under section 1851(i) of the Act for health care items and services furnished to individuals enrolled in a Medicare Advantage plan by health care professionals or facilities not included in the plan's network.

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2. Pursuant to Section 1135(b)(7) of the Act, I hereby waive sanctions and penalties arising from noncompliance with the following provisions of the HIPAA privacy regulations: (a) the requirements to obtain a patient's agreement to speak with family members or friends or to honor a patient's request to opt out of the facility directory (as set forth in 45 C.F.R. § 164.510); (b) the requirement to distribute a notice of privacy practices (as set forth in 45 C.F.R. § 164.520); and (c) the patient's right to request privacy restrictions or confidential communications (as set forth in 45 C.F.R. § 164.522); but in each case, only with respect to hospitals in the designated geographic area that have hospital disaster protocols in operation during the time the waiver is in effect.

3. Pursuant to Section 1135(b)(5), I also hereby modify deadlines and timetables and for the performance of required activities, but only to the extent necessary, as determined by the Centers for Medicare & Medicaid Services, to ensure that sufficient health care items and services are available to meet the needs of individuals enrolled in the Medicare, Medicaid and CHIP programs and to ensure that health care providers that furnish such items and services in good faith, but are unable to comply with one or more of these requirements as a result of the COVID-19 pandemic, may be reimbursed for such items and services and exempted from sanctions for such noncompliance, absent any determination of fraud or abuse.

These waivers and modifications will become effective at 6:00 P.M. Eastern Standard Time on March 15, 2020, but will have retroactive effect to March 1, 2020, nationwide, and continue through the period described in Section 1135(e). Notwithstanding the foregoing, the waivers described in paragraph 2 above are in effect for a period of time not to exceed 72 hours from implementation of a hospital disaster protocol but not beyond the period described in Section 1135(e). The waivers described in paragraphs 1(c) and 2 above are not effective with respect to any action taken thereunder that discriminates among individuals on the basis of their source of payment or their ability to pay.
The waivers and modifications described herein apply in the geographic area covered by the President's proclamation, pursuant to the National Emergencies Act, on March 13, 2020, that the COVID-19 outbreak in the United States constitutes a national emergency; and my January 31, 2020, determination, pursuant to section 319 of the Public Health Service Act, that a public health emergency as a result confirmed cases of 2019 Novel Coronavirus, exists and has existed since January 27, 2020, nationwide.

3/13/2020 /s/

Date Alex M. Azar II

345) 2020-03-14 Zhihuan L: China sending medical team to help Italy contain virus. ChinaDaily 14 March 2020: 1-2. https://www.chinadaily.com.cn/a/202003/14/WS5e6bd352a31012821727f096.html

346) 2020-03-16 Brown BL, McCullough J: Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfusion and Apheresis Science 59 (2020) 102790 : 1-5. https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf

2020-04-14: accepted for publication:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194745/pdf/main.pdf

ABSTRACT

Use of convalescent plasma transfusions could be of great value in the current pandemic of coronavirus disease (COVID-19), given the lack of specific preventative and therapeutic options. This convalescent plasma therapy is of particular interest when a vaccine or specific

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

therapy is not yet available for emerging viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. This report summarizes existing literature around convalescent plasma as a therapeutic option for COVID-19. It also includes recommendations for establishing a convalescent plasma program, enhancement considerations for convalescent plasma, and considerations around pathogen reduction treatment of convalescent plasma. Time is of the essence to set up protocols for collection, preparation, and administration of apheresis-collected convalescent plasma in response to the current pandemic. The immediate use of convalescent plasma provides prompt availability of a promising treatment while specific vaccines and treatments are evaluated and brought to scale. Further development of improved convalescent plasma, vaccines and other therapeutics depends on quick generation of additional data on pathogenesis and immune response. Additionally, given the lack of information around the natural history of this disease, PRT should be considered to add a layer of safety to protect recipients of convalescent plasma.

347) 2020-03-17 Azar A: Declaration under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19. Federal Register, 3/17/2020. https://www.federalregister.gov/documents/2020/03/17/2020-05484/declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical-countermeasures

348) 2020-03-17 Regeneron: Regeneron announces important advances in novel COVID-19 antibody program. https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-important-advances-novel-covid-19-antibody

349) 2020-03-18 Duan K, Liu Bende, Li Cesheng, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X: Effectiveness of convalescent plasma therapy in severe COVID-19 patients. 18 March 2020; PNAS (Proceedings of the National Academy of Sciences of the United States of America) : 1-22. https://www.pnas.org/content/pnas/117/17/9490.full.pdf

Currently, there are no approved specific antiviral agents for novel coronavirus disease 2019 (COVID-19). In this study, 10 severe patients confirmed by real-time viral RNA test were enrolled prospectively. One dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640 was transfused to the patients as an addition to maximal supportive care and antiviral agents. The primary endpoint was the safety of CP transfusion. The second endpoints were the improvement of clinical symptoms and laboratory parameters within 3 d after CP transfusion. The median time from onset of illness to CP transfusion was 16.5 d. After CP transfusion, the level of neutralizing antibody increased rapidly up to 1:640 in five cases, while that of the other four cases maintained at a high level (1:640). The clinical symptoms were significantly improved along with increase of oxyhemoglobin saturation within 3 d. Several parameters tended to improve as compared to pretransfusion, including increased lymphocyte counts (0.65 × 109 /L vs. 0.76 × 109 /L) and decreased C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Radiological examinations showed varying degrees of absorption of lung lesions within 7 d. The viral load was undetectable after transfusion in seven patients who had previous viremia. No severe adverse effects were observed. This study showed CP therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases. The optimal dose and time point, as well as the clinical benefit of CP therapy, needs further investigation in larger well-controlled trials.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

350) 2020-03-18 Trump DJ: Declaring a national emergency concerning the novel coronavirus disease (COVID-19) outbreak. https://www.federalregister.gov/documents/2020/03/18/2020-05794/declaring-a-national-emergency-concerning-the-novel-coronavirus-disease-covid-19-outbreak

351) 2020-03-18 Pharmaceutical Technology: Regeneron identifies several antibodies against Covid-19. https://www.pharmaceutical-technology.com/news/regeneron-covid-19-antibodies/

352) 2020-03-19 Adams J: PSA, If You Are Sick. March 19, 2020. https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/

> As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms--they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider. **We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else.** They will help you think through and learn how to react including figuring out where to go to get tested if necessary.
>
> Dr. Jerome Adams, PSA, If You Are Sick, March 19, 2020.

This PSA makes the assumption that American's have an established PCP's whom they can call but that is not truth:

Fong M: Nearly 1 in 5 Americans haven't seen a doctor in over five years. Onlinedoctor April 14, 2021. https://www.onlinedoctor.com/nearly-1-in-5-americans-havent-seen-a-doctor-in-over-five-years/

CDC: Percentage of having a wellness visit in past 12 months for adults aged 18 and over, United States, 2019. CDC, Centers for Disease Control and Prevention, National Center for Health Statistics: Interactive Summary Health Statistics for Adults—2019. https://wwwn.cdc.gov/NHISDataQueryTool/SHS_adult/index.html

CDC: National Ambulatory Medical Care Survey: 2018 National Summary Tables https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2018-namcs-web-tables-508.pdf

353) 2020-03-19 Simpson BW: COVID-19's stop-gap solution until vaccines and antivirals are ready. Global Health NOW, Johns Hopkins Bloomberg School of Public Health https://www.globalhealthnow.org/2020-03/covid-19s-stop-gap-solution-until-vaccines-and-antivirals-are-ready

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How can plasma be useful against the novel coronavirus?
When you recover from many viral diseases, you have in your blood what are called neutralizing antibodies. These are antibodies that kill the virus. Once you recover, the plasma be taken from donors. It's very safe. It's the same thing as using a blood donation except they don't take the red blood cells, they take the liquid. They take the plasma. It is itself a drug…it can be used for prevention of infection for people who are being exposed or it could be used for therapy for those who are sick.

It's not a vaccine. Think about it as the administration of a protein, it's a liquid that is given to people that gives them immunity.

Right. Because the vaccine would provoke the recipient's antibodies. You'll have the antibodies, but they won't be your antibodies—though it'll do the same thing.
Right.

And if somebody is already sick, can the plasma help them?
Yes, it can be used for prevention or a treatment.

This strategy is already being used in China?
Yes, in fact, the Chinese sent 90 tons of plasma to Italy.

354) 2020-03-20 Zhou G, Chen S, Chen Z: Advances in COVID-19: the virus, the pathogenesis, and evidence-based control and therapeutic strategies. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7171433/pdf/11684_2020_Article_773.pdf

355) 2020-03-20 Healy M: How the blood of coronavirus survivors may protect others from COVID-19. Los Angeles Times 20 March 2020, 1/8. https://www.latimes.com/science/story/2020-03-20/how-blood-from-people-who-survived-covid-19

356) 2020-03-21 Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu Ch, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang QW, Xu SY, Zhu HD, Xu YC, Ji Q, Sharma L, Wang L, Wang J: Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis XX XXXX 2020; XX: 1-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184472/pdf/ciaa310.pdf ; Clin Infect Dis 2020 Jul 28; 71(15): 778-785. https://pubmed.ncbi.nlm.nih.gov/32198501/

357) 2020-03-23 Good/Shutterstock M: World Health Organization warns against untested drugs for COVID-19. Biospace https://www.biospace.com/article/world-health-organization-warns-against-untested-drugs-for-covid-19/

358) 2020-03-23 Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, *et. al.*: The feasibility of convalescent plasma therapy in severe COVID-19 patient: a pilot study. medRxiv Mar 23, 2020; 1 – 21. https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf

359) 2020-03-23 U.S. Food and Drug Adminstration: Emergency Use Authorization. Emergency Use Authorization (EUA) information, and list of all current EUAs.

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https://web.archive.org/web/20200324160355/https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

360) 2020-03-23 Bhandari T: Possible COVID-19 treatment: transfusion of antibodies from recovered patients' blood—Century-old idea applied to modern pandemic. https://medicine.wustl.edu/news/possible-covid-19-treatment-transfusion-of-antibodies-from-recovered-patients-blood/

361) 2020-03-24 Scrip Team: Coronavirus Update: South Korea's Celltrion progresses antibody, Yancopoulos: 'The World is Counting on Us' – Antibody Therapies could ease huge burden on emergency care. Informa Pharma Intelligence https://scrip.pharmaintelligence.informa.com/SC141901/Coronavirus-Update-South-Koreas-Celltrion-Progresses-Antibody-Yancopoulos-The-World-Is-Counting-On-Us

362) 2020-03-24 U.S. Food and Drug Administration: Investigational COVID-19 Convalescent Plasma – Emergency INDs, March 24, 2020.

https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf

- **Eligible patients for use under expanded access provisions:**
  - Must have laboratory confirmed COVID-19
  - Must have severe or immediately life-threatening COVID-19, for example:[1]
    - Severe disease is defined as:
      - dyspnea,
      - respiratory frequency ≥ 30/min,
      - blood oxygen saturation ≤ 93%,
      - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
      - lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening disease is defined as:
      - respiratory failure,
      - septic shock, and/or
      - multiple organ dysfunction or failure
  - Must provide informed consent

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/3

27/3/2020 Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

[1] *Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648*

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<u>NO WHERE</u> in the aforementioned reference #1 by *Wu* and *McGoogan* upon which officially the U.S. FDA based the *Eligibility Criteria* for administration of COVID-19 Convalescent Plasma from March 24, 2020 to September 2, 2020 is "CONVALESCENT", "PLASMA", "ELIGIBILITY" or "CRITERIA" mentioned even once !!!!

2020-03-24 Investigational COVID-19 Convalescent Plasma – Emergency INDs. (This is the NATAP Verbatim internet copy of reference 28 in its entirety that I have copied and pasted verbatim to follow from https://natap.org/2020/COVID/032320_39.htm as this is an original copy I can find on the Internet which is of the FDA's directive of March 24, 2020 that directed all the ***misdirection based on only one reference #1 by Zunyou Wu, M.D., PhD, Jennifer M. McGoogan, PhD which never mentions COVID-19 Convalescent Plasma nor recommends*** the eligibility criteria justifying the FDA authorizations of COVID-19 Convalescent Plasma (CCP), and EUAs that were to follow in the next 10 months.)

PLEASE NOTE THAT WEB SITE REFERENCED JUST BELOW MARCH 24, 2020 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds IS A HYPERLINK THAT BECAUSE OF THE FDA OVERWRITING PRACTICES AS PERMITTED BY THAT WHICH WAS PUBLISHED IN THE *FEDERAL REGISTER* on March 25, 2020 now points *ex post facto* to the future FDA website: Recommendations for Investigational COVID-19 Convalescent Plasma, **February 11, 2021, and then with each overwrite *ad infinitum***. (One can trace back the referenced website with modifications using the *Internet Archive (Wayback Machine* -- https://archive.org/web/) to April 8, 2020. The FDA version of the verbatim document below must have been referenced between March 24, 2020 to ~April 8, 2020 was electronically replaced so that media articles (listed below) referencing the March 24, 2020 announcement *ex post facto* references to April 8, 2020.

*<u>I, therefore, allege that there was **Blantant Misdirection**</u>* **of the official FDA documentation of March 24, 2020 in which the *Eligibility Criteria* is wrongly attributed to reference #1 *which* initiated the administration of CCP TO ONLY EXTREMELY ILL INDIVIDUAL PATIENTS AT THE *WRONG TIME* (<u>not during the early viremic phase</u> or prophylactically) which was probably a <u>Federal Criminal Offense</u> by someone in the FDA, Department of Health and Human Services, and/or *The White House*.**

I allege, on behalf of the American people, this <u>misdirection of official federal FDA</u> documentation facilitated: 1) misdirected CCP application at an inappropriate (wrong) <u>late-in-time</u> in the course of the disease in >700,000 individuals having contracted COVID-19 and having developed life-threatening systemic complications (e.g., bilateral pneumonitis, kidney failure, etc.; 2) promoted nonsensical, inappropriate medical research/NIH ClinicalTrials (https://www.clinicaltrials.gov/ of CCP at the wrong administration time); 3) promoted violation of PL-115-176--*The Right to Try Law*--by promoting NON Completion of Phase I Studies; 4) promoted CCP application late in the individual's COVID-19 disease (which is the WRONG TIME to administer *Passive Immunization*); 5) led to the *de facto* discrediting of *Passive Immunization* as a <u>treatment</u>; 6) promoted *de facto* physician abandonment of their individual COVID-19 positive patients early in the course of the individual's disease (viremic phase); and 7) inadvertently led to greater than a half-of-a-million American deaths!

Below, copied and pasted *verbatim* from the National AIDS Treatment Advocacy Project (NATAP) https://natap.org/2020/COVID/032320_39.htm is the <u>original NATAP copy</u> found of the FDA's directive of March 24, 2020 that directed the ***misdirection*** regarding the eligibility criteria, FDA authorizations of COVID-19 Convalescent Plasma (CCP), and EUAs that were to follow for the next 10 months.

Investigational COVID-19 Convalescent Plasma - Emergency INDs

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

March 24, 2020

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

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- **COVID 19 Convalescent Plasma**

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- Prior diagnosis of COVID-19 documented by a laboratory test
- Complete resolution of symptoms at least 14 days prior to donation
- Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations.
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- **Eligible patients for use under expanded access provisions:**
  - Must have laboratory confirmed COVID-19
  - Must have severe or immediately life-threatening COVID-19, for example:[1]
    - Severe disease is defined as:
      - dyspnea,
      - respiratory frequency ≥ 30/min,
      - blood oxygen saturation ≤ 93%,
      - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
      - lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening disease is defined as:
      - respiratory failure,
      - septic shock, and/or
      - multiple organ dysfunction or failure
  - Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov.
  - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFR 312.305 and 312.310.
  - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
  - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
  - FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
  - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

[1] Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Content current as of:
03/24/2020

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Mr. President:

The article of Wu Z, McGoogan JM*: Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 from the Chinese Center for Disease Control and Prevention IS AN EPIDEMIOLOGY REPORT which NEVER SPEAKS OF THERAPY.* – The U.S. FDA, NIH, CDC, PHS, ORGANIZED, ACADEMIC, AND RESEARCH MEDICINE, etc. MISINTERPRETED this article and APPLIED IT WRONGLY!

–- THE TIMELY LATE ADMINISTRATION OF COVID-19 CONVALESCENT PLASMA AND the antiviral REMDESIVIR became a *de facto* faulty, tragic, DEADLY rationing METHODOLOGY late in the disease of COVID-19 DURING THE CYTOKINE CASCADE AND THE BRADYKININ STORM INSTEAD OF WITHIN <72-120 HOURS OF EARLY VIREMIA FROM THE INITIAL DOCUMENTATION by testing OF AN INDIVIDUAL'S INFECTION AND/OR INITIATION OF SYMPTOMATOLOGY. This U.S. governmental directive by edict regarding ADMINISTRATIVE TIMING OF COVID-19 Convalescent Plasma Therapy and the antiviral Remdesevir WAS ABSOLUTELY LATE and DEADLY WRONG; and it has been contributory in > 1 million deaths from COVID-19 in the U.S.A. over the last two years!

Charles H. Andrus, M.D., F.A.C.S. 5/14/2022
Professor, Department of Surgery, Saint Louis University School of Medicine
Chief, Unit II General Surgery, Surgical Service (112JC), St. Louis VAMC

VA Office phone: 314-652-4100 ext. 54463
Home phone: 314-455-9482
Beeper: 314-491-2417

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

363) 2020-03-24 FDA: Investigational COVID-19 Convalescent Plasma – Emergency INDs. "A licensed physician must request the Emergency IND (eIND) and obtain the COVID-19 convalescent plasma from a blood center. FDA does **not** provide COVID-19 convalescent plasma for eINDs. Investigational COVID-19 Convalescent Plasma – Emergency INDs Frequently Asked Questions (/media/136470/download). [this download now points to: https://www.fda.gov/media/136470/download which is April 3, 2020.].

364) 2020-03-24 U.S. Food and Drug Administration: FDA NEWS RELEASE: Coronavirus (COVID-19) Update: Daily Roundup, March 24, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-24-2020

365) 2020-03-24 Global Biodefense Staff: FDA allows emergency used of investigational convalescent plasma for critical COVID-19 patients. https://globalbiodefense.com/2020/03/24/fda-allows-emergency-use-of-investigational-convalescent-plasma-for-critical-covid-19-patients/

366) 2020-03-24 Desperate for Covid-19 answers, U.S. doctors turn to colleagues in China. STATnews. https://www.statnews.com/2020/03/24/covid-19-answers-doctors-turn-to-china/

367) 2020-03-24 Palca J: FDA Expedites Treatment of Serious Ill COVID-19 Patients with Experimental Plasma. NPR, March 24, 2020. https://www.npr.org/sections/coronavirus-live-updates/2020/03/24/820939536/fda-expedites-treatment-of-seriously-ill-covid-19-patients-with-experimental-pla

368) 2020-03-24 Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y, Zhang S: Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest 24 March 2020: e1-e5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7195335/pdf/main.pdf

369) 2020-03-24 Osborne H: What is convalescent plasma? New York health officials to start trial using blood of people recovered from coronavirus. Newsweek. 24 March 2020: 1-23. https://www.newsweek.com/what-convalescent-plasma-new-york-health-officials-start-trial-using-blood-people-recovered-1493964

370) 2020-03-25 DEPARTMENT OF HEALTH AND HUMAN SERVICES, Food and Drug Administration: **Federal Register** / Vol. 85, No. 58 / Wednesday, March 25, 2020 / Notices. 16949-16950. https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf

371) 2020-03-25 U.S. Food and Drug Adminstration: Emergency Use Authorization. Emergency Use Authorization (EUA) information, and list of all current EUAs. https://web.archive.org/web/20200327194633/https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

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372) 2020-03-25 Regional Platform on Access and Innovation for Health Technologies$_{PRAIS}$, Pan American Health Organization, World Health Organization: FDA: Investigational COVID-19 Convalescent Plasma – Emergency Investigational New Drug Applications, March 25, 2020. https://prais.paho.org/en/fda-investigational-covid-19-convalescent-plasma-emergency-investigational-new-drug-applications/

373) 2020-03-26 Hopkins Tanne J: Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ 2020; 368:m1256 doi: 10.1136bmj.m1256 (Published 26 March 2020). https://www.bmj.com/content/bmj/368/bmj.m1256.full.pdf

Dear Mr. President: *I apologize for copying and pasting the following excerpted as this is copyright protected material by the BMJ Publishing Group Limited but I am presenting this to you as* ***Educational Material*** **BUT** the URL to which the references point were changed by the FDA so that the eligible criteria justifying refererence "[1]" of March 24, 2020 is extremely difficult to find: Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. *–C. Andrus, M.D.*

> Plasma from people who have recovered from covid-19 may contain antibodies to the virus that causes the disease and might be effective against the infection, the FDA said. Convalescent plasma has been studied in outbreaks of other respiratory infections, such as H1N1 influenza, SARS, and MERS. "Although promising, convalescent plasma has not been shown to be effective in every disease studied" and therefore clinical trials were needed to see if it was useful in covid-19, the FDA cautioned.
>
> The FDA told doctors wanting to study the use of convalescent plasma to follow the usual system for an investigational new drug (IND) application.
>
> The plasma must be collected from recovered patients who can donate blood, have had no symptoms for 14 days, and have had negative results on covid-19 tests.
>
> However, given the current public health emergency, the FDA said it was providing emergency access to convalescent plasma for patients "with serious or immediately life threatening covid-19 infections."
>
> Severe disease is defined as dyspnoea, respiratory frequency ≥30 breaths per minute, blood oxygen saturation ≤93%, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2 /FiO2) 50% within 24 to 48 hours.
>
> Life threatening disease is defined as respiratory failure, septic shock, or multiple organ dysfunction or failure. In such cases, doctors can submit a form online or call FDA's hotline telephone number (1-866-300-4374) to get verbal approval for treatment, which is promised within four to eight hours.
>
> Jeffrey Henderson of Washington University School of Medicine in St Louis, Missouri, told National Public Radio, "The FDA just opened the floodgates. Our institution is scrambling to be ready to use this. There are many others, I'm sure." [3]

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

1 FDA. Investigational covid-19 convalescent plasma—emergency INDs. https://www.fda. gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ideprocess-cber/investigational-covid-19-convalescent-plasma-emergency-inds
2 Hixenbaugh M. FDA will allow doctors to treat critically ill coronavirus patients with blood from survivors. NBC News 2020 Mar 24. www.nbcnews.com/news/us-news/fda-will-allowdoctors-treat-critically-ill-coronavirus-patients-blood-n1167831
3 Palca J. FDA expedites treatment of seriously ill covid-19 patients with experimental plasma. National Public Radio, 24 Mar 2020. www.npr.org/sections/coronavirus-liveupdates/2020/03/24/820939536/fda-expedite-treatment-of-seriously-ill-covid-19-patientswith-experimental-plasma

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374) 2020-03-27. Hinton DM: From the EUA update 091 of July 30, 2021. https://www.regeneron.com/downloads/treatment-covid19-eua-fda-letter.pdf https://www.fda.gov/media/145610/download

> On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). [1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

375) 2020-03-27 Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L: Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 Apr 28;323 (16): 1582-1589. https://jamanetwork.com/journals/jama/fullarticle/2763983

376) 2020-03-27 Roback JD, Guarner J: Convalescent plasma to treat COVID-19, Possibilities and challenges. JAMA 2020; 323(16): 1561-1562. https://jamanetwork.com/journals/jama/fullarticle/2763982

377) 2020-03-28 Brunk D: FDA Oks emergency use of convalescent plasma for seriously ill COVID-19 patients. Medscape Medical News. March 28, 2020. https://www.medscape.com/viewarticle/927716

378) 2020-03-29 U.S. Food and Drug Adminstration: Emergency Use Authorization. Emergency Use Authorization (EUA) information, and list of all current EUAs. https://web.archive.org/web/20200330194732/https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

379) 2020-03-30 U.S. Department of Health & Human Services, Centers for Medicare and Medicaid Services: Center for clinical standards and quality/quality, safety and oversight group. Ref: QSO-20-15 Hospital/CAH/EMTALA REVISED.

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https://web.archive.org/web/20200413235000if_/https://www.cms.gov/files/document/qso-20-15-hospital-cah-emtala-revised.pdf

380) 2020-03-30 ACEP COVID-19 Field Guide: EMTALA Regulations and Liability. https://www.acep.org/corona/covid-19-field-guide/regulations-and-liability/emtala/

381) 2020-03-30 Roos D: Before vaccines, doctors 'borrowed' antibodies from recovered patients to save lives –Doctors first tried injecting patients with blood plasma in the early 1900s. The method has been used against diphtheria, the 1918 flu pandemic, measles and Ebola. History Channel Updated Apr 1, 2020. https://www.history.com/news/blood-plasma-covid-19-measles-spanish-flu

382) 2020-03-31 U.S. Food and Drug Administration: Emergency Use Authorization. https://web.archive.org/web/20200331212526/https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

383) 2020-04-01 Weise E, Johnson M: The first US coronavirus patients are being treated with convalescent plasma therapy. Will it work? Not even the doctors know. USA Today 1 Apr 2020: 1-5. https://www.usatoday.com/story/news/health/2020/04/01/coronavirus-plasma-therapy-5-us-patients-covid-19-donors/5090946002/

384) 2020-04 Chen L, Xiong J, Bao L, Shi Y: Convalescent plasma as a potential therapy for COVID-19. The Lancet 2020 April; 20: 398-400. https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30141-9.pdf

385) 2020-04-01 O'Donnell N: BREAKING NEWS: Dr. Fauci on the fight against the virus. https://www.facebook.com/CBSEveningNews/videos/norah-odonnell-should-we-be-advising-people-to-wear-masksdr-anthony-fauci-great-/204826050813336/ 2:10 – 2:48

> Norah O'Donnell: With all due respect it does seem like so much of this we're making it up as we go along.
>
> Dr. Anthony Fauci: Well, you know you make it up as you go along, Norah, because that's what you know—that's where the war is all about. I don't like to necessarily make that analogy to a war, but if you talk to the generals with experience, you have a plan. But when the bullets start flying, everything becomes a fog, and you have to play it by ear. We do have a good plan. We need to be humble that we don't know all the answers, and we don't know how exactly this is going to turn out.
>
> Norah O'Donnell: Dr. Fauci, thank you so very much for your time and expertise.
>
> Dr. Anthony Fauci: It's always good to be with you, Norah. Thank you.

386) 2020-04-02. Cerus: Cerus Corporation announces the inclusion of pathogen reduction technology in the ISBT working party recommendations for the preparation of COVID-19 convalescent plasma. BioSpace https://www.biospace.com/article/releases/cerus-

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corporation-announces-the-inclusion-of-pathogen-reduction-technology-in-the-isbt-working-party-recommendations-for-the-preparation-of-covid-19-convalescent-plasma/

387) 2020-04-02 McCarthy A: Could plasma from recovered COVID-19 patients help others? Boston Children's Hospital. https://answers.childrenshospital.org/covid-19-coronavirus-plasma/

388) 2020-04-03. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JWM, Brüggermann RJ, van der Hoeven H: Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. Pre Prints: Posted Not PEER-reviewed. https://www.preprints.org/manuscript/202004.0023/v1

389) 2020-04-03 Langhi Junior DM, De Santis GC, Bordin JO: COVID-19 convalescent plasma transfusion. ABHH: Associação Brasileira de Hematologia, Hemoterapio e Teopia Celular 3 April 2020: 113-115. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164882/pdf/main.pdf

390) 2020-04-03 FDA: Investigational COVID-19 convalescent plasma – Emergency INDs, Frequently Asked Questions. FDA, 3 April 2020. https://www.fda.gov/media/136470/download

391) 2020-04-03 Mogensen JF: Can COVID-19 be treated? Does blood from survivors help? Experts answer our questions on antibodies. Mother Jones, 1-5. https://www.motherjones.com/politics/2020/04/coronavirus-covid-survivors-treatments-convalescent-plasma-answers/

392) 2020-04-03 Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19. (CDC recommendation started January 31, 2020 to present with last overwriting update feb 16, 2021. http://web.archive.org/web/20200408110417/https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

393) 2020-04-04 Joyner M, (Principal Investigator): COVID-19 expanded access program -- Convalescent Plasma COVID-19 (coronavirus) Treatment – Mayo Clinic. First date digitally preserved by the Internet Archive (Wayback Machine). –Origin of the FDA/Mayo Clinic expanded access program. **(Compassionate Use—can't be used for Randomized Controlled Trials by definition of the NIH and FDA)** https://web.archive.org/web/20200404010134/https://www.uscovidplasma.org/

> The protocol requires the patient or family member to consent to receiving plasma from someone who has recovered from COVID-19. Their plasma has substances that could improve chances of recovery. Only hospitalized patients referred by their health care provider will participate in this protocol.
>
> Hospitalized patients are eligible to receive convalescent plasma if:

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- They are 18+ years of age
- They have laboratory-confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19
- They are admitted to an acute care facility for the treatment of COVID-19 complications
- They have severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
- There is informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:

- Shortness of breath (dyspnea)
- Respiratory frequency ≥ 30/min
- Blood oxygen saturation ≤ 93%
- Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- Lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:

- Respiratory failure
- Septic shock
- Multiple organ dysfunction or failure

Michael J. Joyner, M.D., Summary, Mayo Clinic.
https://www.mayo.edu/research/faculty/joyner-michael-j-m-d/bio-00078027

394) 2020-04-04 O'Donnell R: Before Dr. Anthony Fauci was the leading Covid-19 expert, he was captain of his high school basketball team. SBNATION
https://www.sbnation.com/nba/2020/4/4/21207982/dr-anthony-fauci-coronavirus-covid-19-expert-high-school-basketball-team

395) 2020-04-06 Xinhua: Timeline of China releasing information on COVID-19 and advancing international cooperation. ChinaDaily, 6 April 2020: 1-3.
https://www.chinadaily.com.cn/a/202004/06/WS5e8b2f5aa31012821728496b.html

396) 2020-04-06 Ledger K: Convalescent plasma: A therapy for COVID-19. Discovery's Edge—Mayo Clinic's Research Magazine 6 April 2020: 1-4.
https://discoverysedge.mayo.edu/2020/04/06/convalescent-plasma-a-therapy-for-covid-19/

397) 2020-04-06 CSL Behring: Global plasma leaders collaborate to accelerate development of potential COVID-19 hyperimmune therapy. 6 April 2020: 1-6.
https://www.cslbehring.com/newsroom/2020/covid-19-hyperimmune (Kennedy DB, Vice

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President – North America Medical Affairs : A letter from CSL Behring, form-letter email 6 April 2020: 1-2).

398) 2020-04-07 Bloch EM, Shoham S, Casadevall A, Sachals BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JR, A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski L, Bailey JA, Tobian AAR: Deployment of convalescent plasma for the prevention and treatment of COVID-19. https://www.jci.org/articles/view/138745

> *…Convalescent plasma has also been used in the COVID-19 pandemic; limited data from China suggest clinical benefit, including radiological resolution, reduction in viral loads, and improved survival….*

399) 2020-04-07 Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. Jama April 7, 2020; 323(13): 1239-1242. https://jamanetwork.com/journals/jama/fullarticle/2762130 (reference first released in Feb 2020, **ref. 326** above on 2020-02-24).

400) 2020-04-07 Miller H: Mayo Clinic CEO says convalescent plasma could be effective treatment for coronavirus. CNBC, Apr 7, 2020. https://www.cnbc.com/2020/04/07/mayo-clinic-ceo-says-convalescent-plasma-could-be-effective-treatment-for-coronavirus.html

401) 2020-04-07 Rivera N: Medical Task Force COVID-19 (Puerto Rico): Investigational COVID-19 Convalescent Plasma Emergency Investigational New Drug, Date April 7, 2020. https://covid19tf.rcm.upr.edu/wp-content/uploads/sites/45/2020/04/Protocolo28-Convalescent-Plasma-1.pdf

> Since only limited data exits at this moment regarding the effectiveness of this therapy, it cannot be routinely recommended or use as a proven treatment option. The Food and Drug Administration (FDA) has provided several pathways to administer or study the use of convalescent plasma in COVID-19 patients:
> • Clinical Trials: Investigators wishing to study the use of convalescent plasma need to submit a request to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).
> • Expanded Access: FDA is working with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 convalescent plasma. For patients with, or at risk of, severe or life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials, access may be available through participation of acute care facilities in an investigational expanded access protocol under an IND already in place.
> • Single Patient Emergency IND: For patents who are not able to participate in a clinical trial or in an expanded access program, given the public health emergency FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient's physician requesting a single patient emergency Investigational New Drug Application (eINDs) for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This eIND process is not for the use of COVID-19 convalescent plasma for the prevention of infection.

402) 2020-04-08 Xinhua: Timeline of China releasing information on COVID-19 and advancing international cooperation. ChinaDaily 8 April 2020: 1-5. https://global.chinadaily.com.cn/a/202004/08/WS5e8d0abaa310aeaeeed509be.html

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403) 2020-04-08 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. April 8, 2020. https://web.archive.org/web/20200413010215/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

> ***Patient Eligibility***
>
> *To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment ProtocolExternal Link Disclaimer. These criteria include:*
>
> - *Laboratory confirmed COVID-19*
> - *Severe or immediately life-threatening COVID-19, for example,*
>   - *Severe disease is defined as one or more of the following:*
>   - *shortness of breath (dyspnea),*
>   - *respiratory frequency ≥ 30/min,*
>   - *blood oxygen saturation ≤ 93%,*
>   - *partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,*
>   - *lung infiltrates > 50% within 24 to 48 hours*
>   - *Life-threatening disease is defined as one or more of the following:*
>   - *respiratory failure,*
>   - *septic shock,*
>   - *multiple organ dysfunction or failure*
> - *Informed consent provided by the patient or healthcare proxy.*

404) 2020-04-08 FDA: Recommendations for Investigational COVID-19 Convalescent Plasma. https://web.archive.org/web/20200408215026/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma which hyperlinked on 4/8/2020 to that which follows on 4/14/2020.

405) 2020-04-08 Pharmabiz.com: Global plasma leaders collaborate to speed up development of potential COVID-19 hyperimmune therapy. Pharmabiz.com, Osaka, Japan, Wednesday, April 8, 2020. http://www.pharmabiz.com/PrintArticle.aspx?aid=122309&sid=2

406) 2020-04-08 Spencer G: A promising COVID-19 treatment gets fast-tracked. Johns Hopkins University HUB 8 April 2020: 1-9. https://hub.jhu.edu/2020/04/08/arturo-casadevall-blood-sera-profile/

407) 2020-04-11 Robson B: COVID-19 Coronavirus spike protein analysis for synthetic analysis for synthetic vaccines, a peptidomimetic antagonist, and therapeutic drugs, and analysis of a proposed achilles' heel conserved region to minimize probability of escape

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mutations and drug resistance. Comput Biol Med 11 Apr 2020, 1-57. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151553/pdf/main.pdf

408) 2020-04-11 Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, Rojas-Villarraga A, Ramírez-Santana C, Díaz-Coronado JC, Manrique R, Mantilla RD, Shoenfeld Y, Anaya JM: Convalescent plasma in COVID-19: Possible mechanisms of action. Autoimmunity Reviews. 11 April 2020; 1-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7198427/pdf/main.pdf

409) 2020-04-12 Anadolu Agency: Good response for COVID-19 plasma treatment: Red Crescent head. Hurriyet Daily News https://www.hurriyetdailynews.com/good-response-for-covid-19-plasma-treatment-red-crescent-head-153776

410) 2020-04-13 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. April 13, 2020. https://web.archive.org/web/20200430055722/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

411) 2020-04-13 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry. **The original version of this directive for the Industry was issued and labelled as April 2020. The initial version of April 2020 for the Industry published for the website on which this was published can no longer be found on the Internet and the Internet Archive's first capture was April 14, 2020 of the revision version of April 13, 2020:**
https://web.archive.org/web/20200414181056/https://www.fda.gov/media/136798/download

Ongoing on official FDA website URL below has been overwritten many times and captured (132 captures) by the Internet Archive from 14 Apr 2020 to 11 Mar 2022 per the Wayback Machine of the Internet Archive is: https://www.fda.gov/media/136798/download

As I printed out the original version of this document that is labelled April 2020 (I assume sometime prior to April 13, 2020), I realized that original version cannot be found on the Internet. Therefore, **I have scanned and attached here my personal copy of the following to be forever recorded in history as the Original FDA version of:**

Investigational COVID-19
Convalescent Plasma

Guidance for Industry

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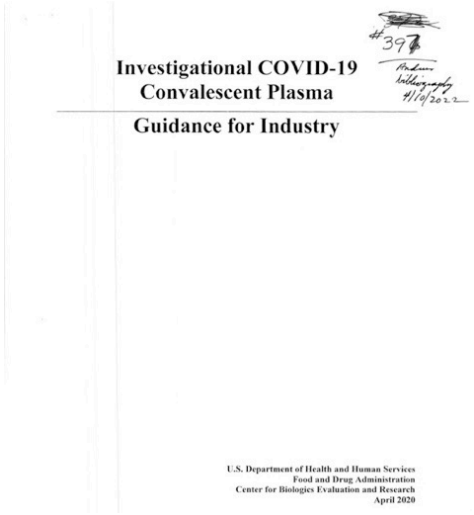
Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
April 2020

(As you will note, **the FDA already had recognized its error** of the FDA March 24, 2020, in that in its initial announcement of COVID-19 Convalescent Plasma as an Investigational drug the FDA had stipulated that COVID-19 Convalescent Plasma was **to be given only** to the very serious ill patients (late in the Cytokine Cascade and the Bradykinin Storm instead of early in the viremia) **erroneously interpretating the Chinese epidemiology journal report[385] regarding 72314 cases as a treatment directive (which it was not)**!). As a lie of omission which went unnoticed, the FDA removed the late recommendations of administration from all its documentations regarding COVID-19 Convalescent Plasma beginning on September 2, 2020. ***Please compare eligibility critera for same FDA documents of*** reference 546 of September 1, 2020 versus 547 of September 2, 2020 that follow.—**THE ELIGIBILITY REQUIREMENTS FOR LATE ADMINISTRATION WERE REMOVED BY SOMEONE IN THE FDA.**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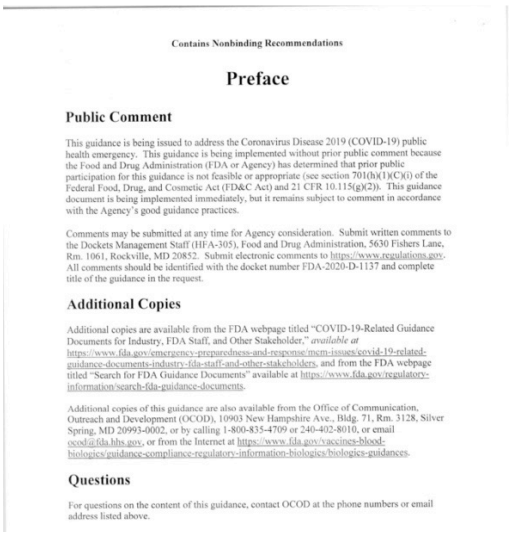

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Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1137 and complete title of the guidance in the request.

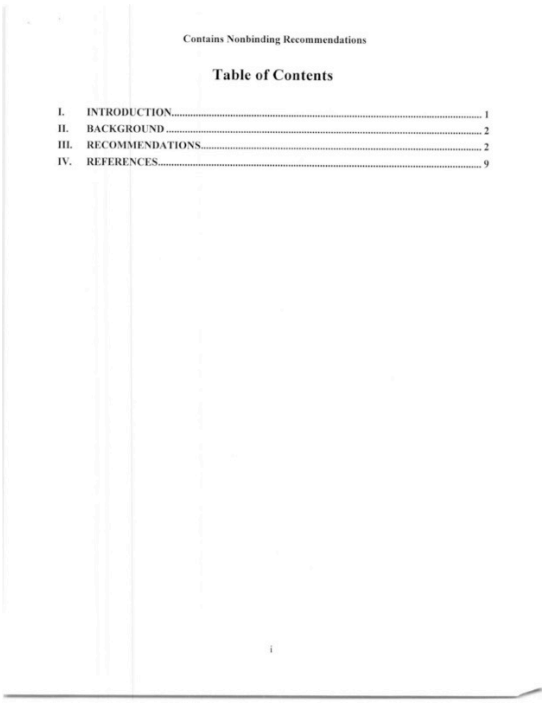
Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholder," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, and from the FDA webpage titled "Search for FDA Guidance Documents" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Additional copies of this guidance are also available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

Questions

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.



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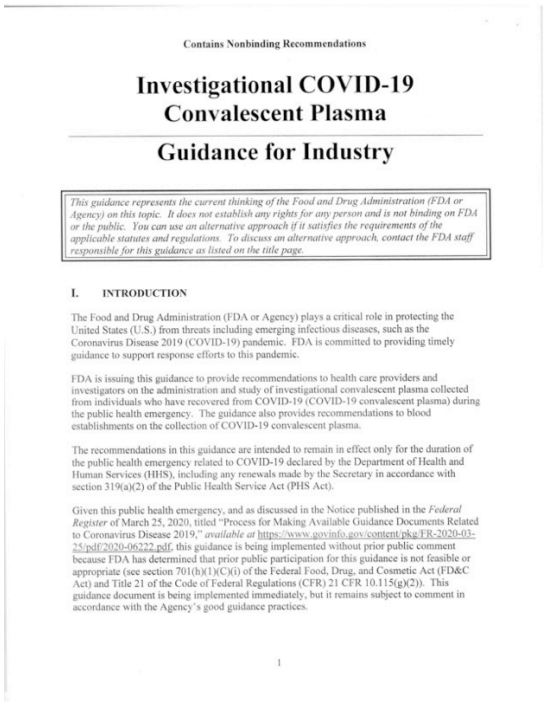

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Investigational COVID-19 Convalescent Plasma

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States (U.S.) from threats including emerging infectious diseases, such as the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. The guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

The recommendations in this guidance are intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services (HHS), including any renewals made by the Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act).

Given this public health emergency, and as discussed in the Notice published in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21 of the Code of Federal Regulations (CFR) 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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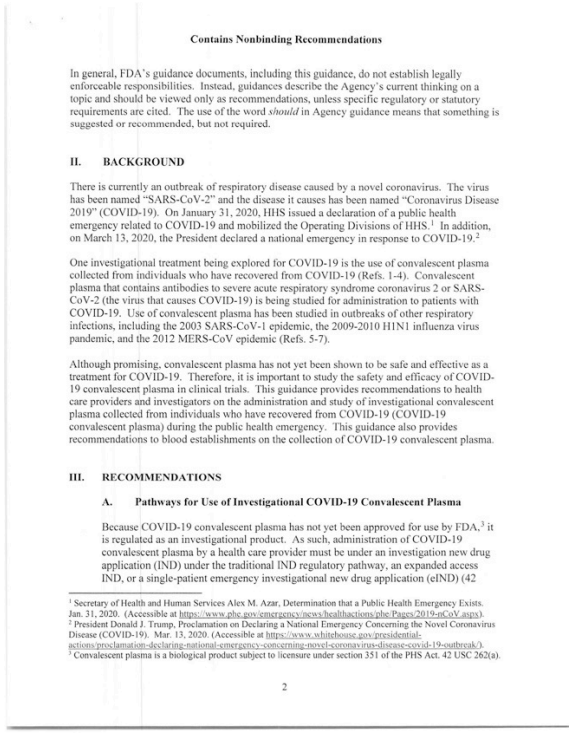

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In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[2]

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19 (Refs. 1-4). Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic (Refs. 5-7).

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials. This guidance provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. This guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

III. RECOMMENDATIONS

A. Pathways for Use of Investigational COVID-19 Convalescent Plasma

Because COVID-19 convalescent plasma has not yet been approved for use by FDA,[3] it is regulated as an investigational product. As such, administration of COVID-19 convalescent plasma by a health care provider must be under an investigation new drug application (IND) under the traditional IND regulatory pathway, an expanded access IND, or a single-patient emergency investigational new drug application (eIND) (42

[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx).
[2] President Donald J. Trump, Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19). Mar. 13, 2020. (Accessible at https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/).
[3] Convalescent plasma is a biological product subject to licensure under section 351 of the PHS Act. 42 USC 262(a).

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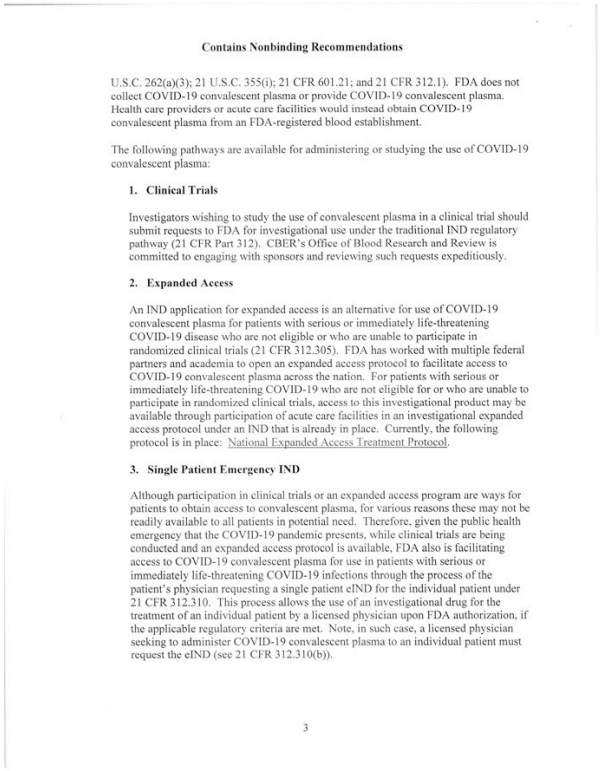

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U.S.C. 262(a)(3); 21 U.S.C. 355(i); 21 CFR 601.21; and 21 CFR 312.1). FDA does not collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma. Health care providers or acute care facilities would instead obtain COVID-19 convalescent plasma from an FDA-registered blood establishment.

The following pathways are available for administering or studying the use of COVID-19 convalescent plasma:

1. Clinical Trials

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). CBER's Office of Blood Research and Review is committed to engaging with sponsors and reviewing such requests expeditiously.

2. Expanded Access

An IND application for expanded access is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CFR 312.305). FDA has worked with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 convalescent plasma across the nation. For patients with serious or immediately life-threatening COVID-19 who are not eligible for or who are unable to participate in randomized clinical trials, access to this investigational product may be available through participation of acute care facilities in an investigational expanded access protocol under an IND that is already in place. Currently, the following protocol is in place: National Expanded Access Treatment Protocol.

3. Single Patient Emergency IND

Although participation in clinical trials or an expanded access program are ways for patients to obtain access to convalescent plasma, for various reasons these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the COVID-19 pandemic presents, while clinical trials are being conducted and an expanded access protocol is available, FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient's physician requesting a single patient eIND for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met. Note, in such case, a licensed physician seeking to administer COVID-19 convalescent plasma to an individual patient must request the eIND (see 21 CFR 312.310(b)).

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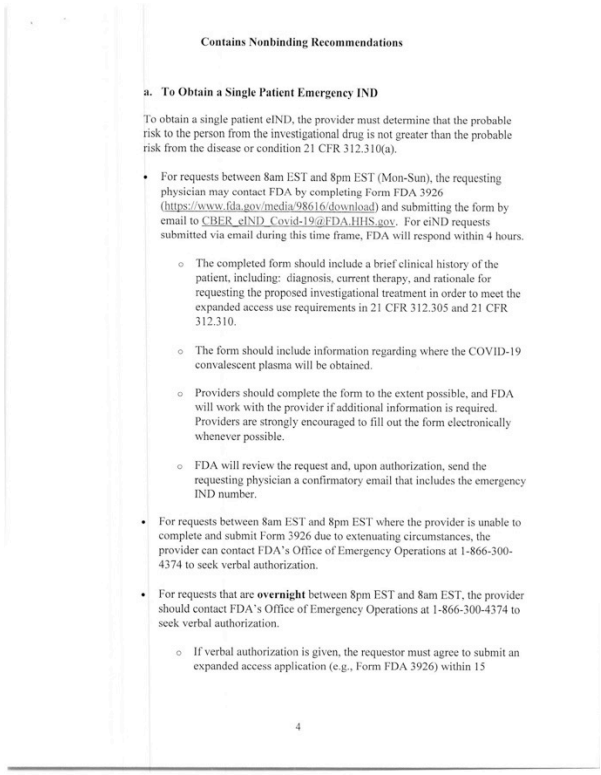

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a. To Obtain a Single Patient Emergency IND

To obtain a single patient eIND, the provider must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition 21 CFR 312.310(a).

- For requests between 8am EST and 8pm EST (Mon-Sun), the requesting physician may contact FDA by completing Form FDA 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov. For eIND requests submitted via email during this time frame, FDA will respond within 4 hours.
    - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements in 21 CFR 312.305 and 21 CFR 312.310.
    - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
    - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required. Providers are strongly encouraged to fill out the form electronically whenever possible.
    - FDA will review the request and, upon authorization, send the requesting physician a confirmatory email that includes the emergency IND number.
- For requests between 8am EST and 8pm EST where the provider is unable to complete and submit Form 3926 due to extenuating circumstances, the provider can contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
- For requests that are **overnight** between 8pm EST and 8am EST, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
    - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., Form FDA 3926) within 15

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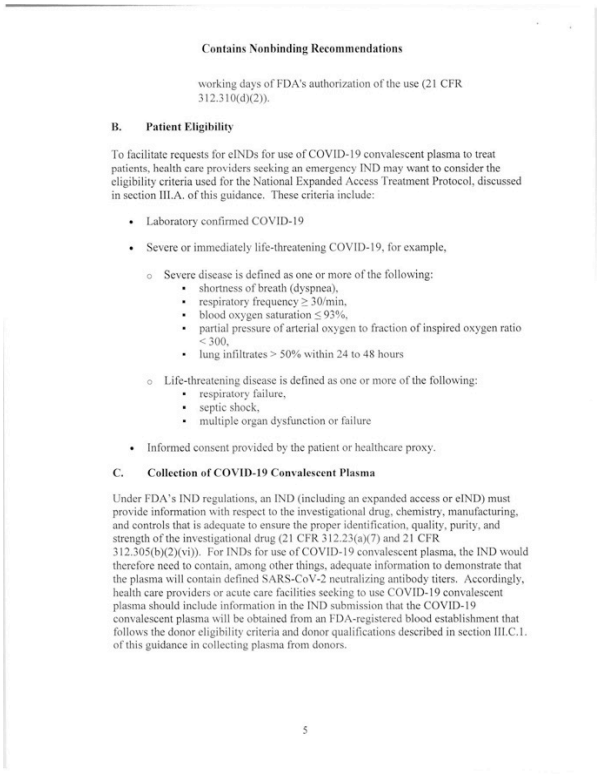

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working days of FDA's authorization of the use (21 CFR 312.310(d)(2)).

B. Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol, discussed in section III.A. of this guidance. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
  - Severe disease is defined as one or more of the following:
    - shortness of breath (dyspnea),
    - respiratory frequency ≥ 30/min,
    - blood oxygen saturation ≤ 93%,
    - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
    - lung infiltrates > 50% within 24 to 48 hours
  - Life-threatening disease is defined as one or more of the following:
    - respiratory failure,
    - septic shock,
    - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

C. Collection of COVID-19 Convalescent Plasma

Under FDA's IND regulations, an IND (including an expanded access or eIND) must provide information with respect to the investigational drug, chemistry, manufacturing, and controls that is adequate to ensure the proper identification, quality, purity, and strength of the investigational drug (21 CFR 312.23(a)(7) and 21 CFR 312.305(b)(2)(vi)). For INDs for use of COVID-19 convalescent plasma, the IND would therefore need to contain, among other things, adequate information to demonstrate that the plasma will contain defined SARS-CoV-2 neutralizing antibody titers. Accordingly, health care providers or acute care facilities seeking to use COVID-19 convalescent plasma should include information in the IND submission that the COVID-19 convalescent plasma will be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications described in section III.C.1. of this guidance in collecting plasma from donors.

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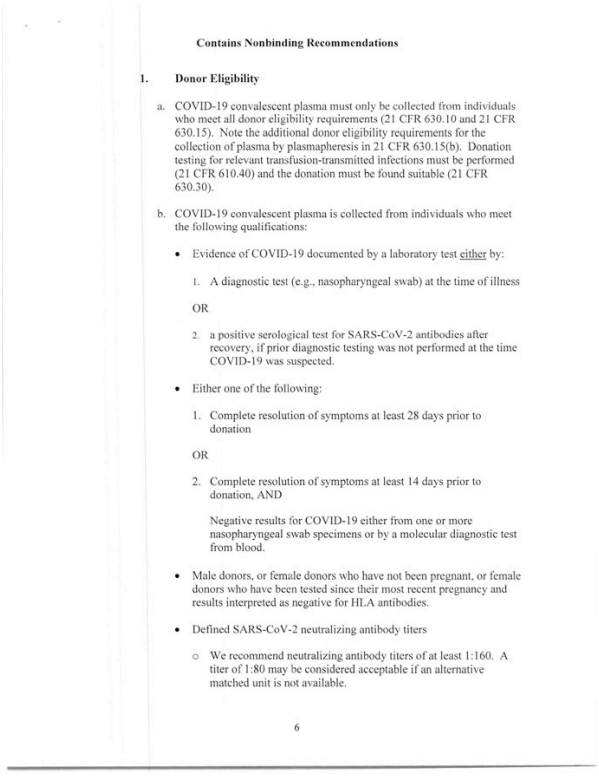

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1. Donor Eligibility

a. COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15(b). Donation testing for relevant transfusion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

b. COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:

- Evidence of COVID-19 documented by a laboratory test either by:
  1. A diagnostic test (e.g., nasopharyngeal swab) at the time of illness

  OR

  2. a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.
- Either one of the following:
  1. Complete resolution of symptoms at least 28 days prior to donation

  OR

  2. Complete resolution of symptoms at least 14 days prior to donation, AND

     Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.
- Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
- Defined SARS-CoV-2 neutralizing antibody titers
  - We recommend neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

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- NOTE: If neutralizing antibody titers cannot be obtained in advance, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.

Registered and licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their license or obtain their own IND to collect and manufacture COVID-19 convalescent plasma for investigational use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulation, and 2) collect plasma from individuals that meet the donor qualifications specified above, which would be included in the applicable IND(s) held by a health care provider or other sponsor.

Once manufactured, the COVID-19 convalescent plasma may be distributed for investigational use.

Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

2. Labeling

a. The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use" (21 CFR 312.6(a)).

   In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

   i. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.

b. We recommend the use of a uniform container label for COVID-19 convalescent plasma. In particular, we recommend the use of the International Society of Blood Transfusion (ISBT) format specified in the United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.

c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection,

stored at -18C or colder and have an expiration date one year from the date of collection.

D. Recordkeeping

A health care provider who is participating in an IND, including an expanded access IND or eIND, must maintain records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patient (21 CFR 312.62). Such records should include the unique identification number(s) (e.g., the ISBT donation identification number(s)) of the unit(s).

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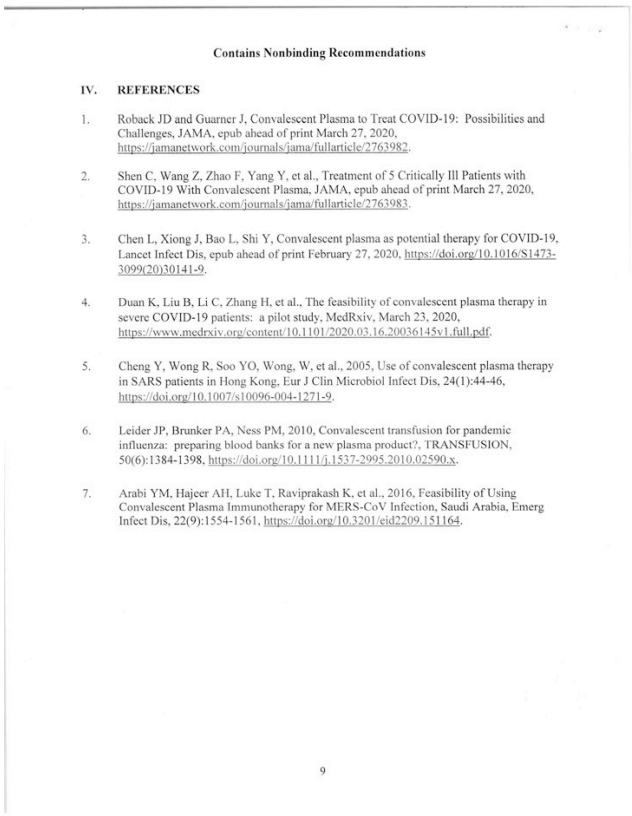

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9

412) 2020-04-13 Gibson Dunn: FDA round-up: Overview of emergency actions to expedite the availability of medical products to combat COVID-19, April 13, 2020. https://www.gibsondunn.com/wp-content/uploads/2020/04/fda-round-up-overview-of-emergency-actions-to-expedite-the-availability-of-medical-products-to-combat-covid-19.pdf Pages 14 – 15.

i. There are no FDA-approved drugs or vaccines to treat or cure COVID-19, but at the end of March, FDA launched the Coronavirus Treatment Acceleration Program (CTAP), a special emergency program to expedite the development of COVID-19 therapies. The CTAP program is using "every tool at the agency's disposal" to provide "ultra-rapid, interactive input."[41] FDA has turned around reviews on COVID-19 development plans within 24 hours and completed reviews of single-patient expanded-access requests within three hours. FDA has redeployed medical and regulatory staff to serve on review teams dedicated to COVID-19 therapies. FDA also has streamlined the process for developers and physicians to contact FDA with inquiries and to submit requests for the emergency use of investigational products. FDA is prioritizing these requests based on factors such as the product's scientific merits and the stage of development. In addition to clinical studies, FDA is looking at real-world data sources to inform its evaluation of potential

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therapies, and FDA is leveraging scientific information being generated in China, Italy, Japan, and South Korea.

ii. According to FDA, there are currently 10 therapeutic agents in active trials and 15 therapeutic agents in planning stages, and the Agency will publish updates as these therapies progress through the development process. Examples of potential therapies and vaccines include the following:

1.) Remdesivir. Remdesivir is an investigational broad-spectrum antiviral treatment, which was previously tested to treat diseases caused by other coronaviruses, such as Ebola. FDA has been working with Gilead Sciences, Inc. to expedite the clinical studies of remdesivir in adults diagnosed with COVID-19 and to permit the emergency use of the drug through an expanded access program. In March, Gilead began enrolling patients in two Phase 3, randomized, open-label, multicenter clinical studies. One of the studies will evaluate the safety and efficacy of two dosing durations in addition to the standard of care for patients with severe COVID-19. The other study will evaluate the same dosing regimens in addition to the standard of care for patients with moderate COVID-19. Other ongoing studies of remdesivir include the NIAID Phase 2 adaptive, randomized, double-blind, placebo-controlled trial and studies in China and France.

2.) Convalescent Plasma. Convalescent plasma, collected from individuals who have recovered from COVID-19, contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19). Use of convalescent plasma as a therapeutic agent has been studied in prior outbreaks of respiratory infections, such as the H1N1 influenza pandemic. Earlier this month, FDA entered a collaboration with BARDA, the American Red Cross, and the Mayo Clinic to simplify the process for health care providers to collect, distribute, and use convalescent plasma in patients. As a result of this collaboration, FDA estimates that thousands of units of plasma will be available to patients within the coming weeks. FDA also is working with NIAID to coordinate a study of hyperimmune globulin, which is a biological product manufactured from convalescent plasma.

iii. On April 8, 2020, FDA issued guidance on the administration and study of investigational convalescent plasma during the public health emergency.[42] Prior to this guidance, FDA had approved emergency INDs for the use of convalescent plasma in very ill COVID-19 patients. The guidance provides recommendations regarding the regulatory pathways for using investigational COVID-19 convalescent plasma, patient eligibility, the collection of COVID-19 convalescent plasma from donors, labeling, and record-keeping. In addition to the traditional IND pathway (21 C.F.R. Part 312), convalescent plasma may be permitted for investigational use through an expanded access IND for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 C.F.R. § 312.305) or through single patient emergency INDs following the request by a licensed physician (21 C.F.R. § 312.310). The convalescent plasma should be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications. Donors should have complete resolution of symptoms at least 28 days prior to donation or complete resolution of symptoms at least 14 days prior to donation and negative COVID-19 test results. FDA is relaxing requirements relating to the registration, licensure, and procedures of blood establishments that collect and distribute the convalescent plasma for investigational use.

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413) 2020-04-13 CBS Evening News with Norah O'Donnell: Racing to a Cure. https://www.viacomcbspressexpress.com/cbs-news-and-stations/releases/print?id=54995

414) 2020-04-14 FDA first document of Guidance for industry. [U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry] https://web.archive.org/web/20200414181056/https://www.fda.gov/media/136798/download

415) 2020-04-14 Pardo J, Shukia AM, Chamarthi G, Gupte A: The journey of remdesivir: from Ebola and COVID-19. Drugs in Context 2020 Apr 14; 9: 1-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250494/pdf/dic-2020-4-14.pdf

416) 2020-04-16 Komaroff AL: Reviewing Duan K *et al Proc Natl Acad Sci USA 2020 Apr 6*: Convalescent plasma therapy in patients with severe COVID-19. NEJM Journal Watch 16 April 2020: 5-6. https://www.jwatch.org/na51335/2020/04/16/convalescent-plasma-therapy-patients-with-severe-covid-19.

417) 2020-04-16 Cox D: The blood of coronavirus survivors could help tackle the pandemic. Wired, Wight Hosting, April 16, 2020. https://www.wired.co.uk/article/coronavirus-blood-plasma-trials

418) 2020-04-16. Wired, News Archives UK: The blood of coronavirus survivors could help cope with the pandemic. https://www.wired.co.uk/article/coronavirus-blood-plasma-trials The following was copied verbatim for documentation at the time of how China stopped there COVID-19 epidemic:

i. *In late January, hospitals across China began using convalescent plasma as a treatment for Covid-19, and in recent weeks other countries have followed suit after the publication of initial results from Wuhan and Shanghai. While these trials involved just a small handful of patients, they received global attention as they appeared to demonstrate that convalescent plasma could aid recovery in even the most critically ill patients.*

ii. *"This is amazing because the vast majority of people thought that convalescent plasma could only be effective if administered early in the disease course," says Daniele Focosi, a transfusion specialist at Pisa University Hospital in Italy. "But the Chinese case series has proved clinical benefit even at a late stage which is very intriguing because it could be a life saving treatment."*

iii. *As of April 6, it was reported that 19 clinical trials of convalescent plasma are already taking place in China, the US, Italy, Iran, Mexico, and Colombia, with more planned. This week Italy is launching a nationwide initiative co-ordinated by Focosi's team at Pisa University Hospital which will use convalescent plasma in hospitals across five more of Italy's 20 regions, complementing an existing trial taking place in Lombardy, the epicentre of the Italian outbreak.*

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iv. *In the UK, the NHS is currently seeking donors for two trials of its own which will compare convalescent plasma against other experimental medications such as antiviral drugs. "One of these trials is to treat patients with Covid-19 pneumonia who have not reached the stage of ventilation to try to stop that happening," says David Tappin, of the University of Glasgow School of Medicine, who is looking to obtain approval to run his own trial looking at whether convalescent plasma can help protect NHS workers. "The other is to treat severely ill patients already ventilated to try to reduce time on ventilators and to reduce death."*

v. *But finding suitable donors is not as straightforward as it might seem. While there are more than 400,000 people around the world who have recovered from Covid-19, the rapid mutation rate of the virus as it has passed between countries means that donors have to be sourced locally. As the pandemic in Italy worsened last month, China reportedly offered to ship 90 tons of convalescent plasma to Italian hospitals for emergency use, but tests soon showed that it could not be used.*

vi. *"We have evidence that the envelope protein called the spike protein is mutating," says Focosi, who is one of the co-investigators leading the new multi-centre trial in Italy. "So convalescent plasma collected in China may not be protective for Covid-19 patients in Europe and the US. You need antibodies derived from infection to the same strain which is circulating in your area."*

419) 2020-04-17 Langi DM, Jr., De Santis GC, Bordin JO: Covid-19 convalescent plasma transfusion. Hematol Transfus Cell Ther. 2020 Apr-Jun; 42(2): 113 – 115. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164882/pdf/main.pdf

i. … Therefore, all therapeutic options for the potentially lethal COVID-19 infection must be discussed ethically and scientifically. Historically, convalescent plasma (CP), a passive immunotherapy, has been used as a possible therapeutic option when no proven specific vaccine or drug is available for emerging infections.1,2 The administration of convalescent plasma or immunoglobulins has been shown to shorten the hospital stay and reduce the mortality rate in patients with SARS who did not respond to methylprednisolone in uncontrolled non-randomized clinical trials.3,4 Cheng et al. investigated 1775 SARS patients and found that 80 patients transfused with SARS convalescent plasma had a lower mortality rate, compared to non-transfused patients (12.5% vs. 17%).[4]

ii. Conclusions:

iii. Analogous to the SARS, the COVID-19 infection progresses with an intense inflammatory response that eventually causes serious lung damage, increasing the mortality risk. In the absence of a definitive curative management, many treatment algorithms have been explored in the treatment of the COVID19. Among possible interventions, the use of plasma collected from recovered patients shows an initial promise, however published results of rigorous clinical trials are needed before we may draw definitive effectiveness conclusions on this passive antibody therapy.

iv. The administration of the COVID-19 convalescent plasma must, however, fulfill some requirements related to availability of COVID-19 recovered donors: well-designed study protocols to guarantee the efficacy analysis of such an intervention; governmental and institutional compliance, and; laboratory support to perform serological and molecular assays, including the measurement of viral neutralization and immune response.[11] In addition, the connection between hospitals, blood centers and the plasma industry must follow flawless strategies, as plasma units may be frozen before distribution or be manufactured as concentrated COVID-19 immunoglobulin.

420) 2020-04-17 Gottlieb S: Former FDA chief Gottlieb explains the potential of Gilead's Covid-19 treatment. (The Antiviral Remdesivir) https://www.cnbc.com/video/2020/04/17/gottlieb-treatment-gilead-clinical-trials-covid-19-squawk-box.html

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Prevention: *Active Immunization*: Vaccines

421) 2020-04-20 Cheen L, Xiong J, Bao L, Shi Y: Convalescent plasma as a potential therapy for COVID-19. www.thelancet.com/infection April 2020; 20: 398-400. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7128218/pdf/main.pdf

422) 2020-04-22 Fleming AB, Raabe V: Current studies of convalescent plasma therapy for COVID-19 may underestimate risk of antibody-dependent enhancement. J Clinical Virology 28 April 2020; 127: 104388. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7187833/pdf/main.pdf ***[While ADE (antibody dependent enhancement) is theoretically possible has been reported in the treatment of Dengue fever, it has not been observed or reported in the utilization of COVID-19 Convalescent Plasma in the thousands of patients that have received CCP in the last year and a half.].***

> …The first case series describing the use of convalescent plasma to treat critically-ill patients with COVID-19 showed clinical improvement and a decline in viral load in all treated patients , serving as a proof-on-concept for this strategy…
>
> 1. This shift may have a greater impact on disease severity if antibodies are present early in the course of infection. …
>
> Current studies of convalescent plasma are limited by lack of representation of patients in the early phase of infection, as well as confounding from multiple concurrent therapies and small patient numbers. …

423) 2020-04-23 Dzik S: COVID-19 Convalescent Plasma: Now is the time for better science. Transfusion Medicine Reviews 34 (2020141-144. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177063/pdf/main.pdf

424) 2020-04-23 Seghatchian J, Lanza F: Convalescent plasma, an apheresis research project targeting and motivating the fully recovered COVID-19 patients: A rousing message of clinical benefit to both donors and recipients alike. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177094/pdf/main.pdf

425) 2020-04-24 Trump D: Donald Trump Coronavirus press conference transcript April 24. Rev Apr 24, 2020. https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-24 The discussion of intravenous disinfectants overshadowed the conference in which Dr. Hahn mentioned Convalescent Plasma and other anti-viral therapies. BBC: Coronavirus: Outcry after Trump suggests injecting disinfectant as treatment. 24 April 2020. https://www.bbc.com/news/world-us-canada-52407177

426) 2020-04-27 van de Veerdonk FL, Netea MC, van Deuren M, van der Meer JWM, de Mast Q, Brüggemann RJ, van der Hoeven H: Kallikrein-kinin blockade in patients with COVID 19 to prevent acute respiratory distress syndrome. eLife 2020; 9 e57555. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7213974/pdf/elife-57555.pdf

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427) 2020-04-28 Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X: Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS April 28, 2020; 117 (17): 9490-9496. https://www.pnas.org/content/pnas/117/17/9490.full.pdf

428) 2020-04-28 Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP: The trinity of COVID-19: immunity, inflammation and intervention. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7187672/pdf/41577_2020_Article_311.pdf

429) 2020-04-28 Zhu M, Hu K, Zhu Z: Use of convalescent plasma in COVID-19 patients in China. Transfusion Clinique et Biologique 28 April 2020: 1-2. https://www.em-consulte.com/showarticlefile/1367091/main.pdf

430) 2020-04-28 NCR Editorial Staff: Editorial: Dolan delivers the church to Trump and the GOP. National Catholic Reporter Apr 28, 2020. https://www.ncronline.org/news/opinion/editorial-dolan-delivers-church-trump-and-gop

431) 2020-04-29 Herper M, Feuerstein A: Critical study of Gilead's Covid-19 drug show patients are responding to treatment, NIH says. Statnews 29 Apr 2020: 1-8. https://www.statnews.com/2020/04/29/gilead-says-critical-study-of-covid-19-drug-shows-patients-are-responding-to-treatment/

432) 2020-04-29 Fung K: Dr. Fauci says remdesivir trial shows drug has promise as FDA plans to announce emergency use. Newsweek 29 Apr 2020: 1-10. https://www.newsweek.com/dr-fauci-says-remdesivir-trial-shows-drug-has-promise-fda-plans-announce-emergency-use-1501028

433) 2020-04-29 Gittleson B: Trump, Fauci tout 'good news' from remdesivir drug trial in treating COVID-19. ABCNews 29 Apr 2020. https://abcnews.go.com/Politics/trump-fauci-tout-good-news-remdesivir-drug-trial/story?id=70407208

434) 2020-04-29 Lovelace B: Dr. Anthony Fauci says Gilead's remdesivir will set a new 'standard of care' for coronavirus treatment. CNBC. https://www.cnbc.com/2020/04/29/dr-anthony-fauci-says-data-from-remdesivir-coronavirus-drug-trial-shows-quite-good-news.html

435) 2020-04-29 Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C: Immune response in COVID-19: Addressing a pharmacological challenge by targeting pathways triggered by SARS-Co V-2. Nature 29 May, 2020; 5:84: 1-3. https://www.nature.com/articles/s41392-020-0191-1.pdf

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436) 2020-04-29 Xi A, Zhuo M, Dai J, Ding Y, Ma X, Ma X, Wang X, Shi L, Bai H, Zheng H, Nuermberger E, Xu J: Epidemiology and clinical characteristics of discharge infected with SARS-CoV-2 on the Qinghai Plateau. J Medical Virology May 21, 2020; 92(11): 2528-2535. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.26032

> Thus, our 3 severe patients were given convalescent plasma (50 ml, qod, twice) collected form 2 patients who had recovered from COVID-19. We detected SARS-CoV-2 antibodies (IgG and IgM) from the convalescent plasma of one donated patient using chemiluminescent immunoassay. The level of IgG was very high (>30 AU/ml) and 1gG (1:80) was 3,464 AU/mL. As expected, the level of IgM was very low (0.093 AU/mL). the CT images, blood gas analysis and symptoms improved the convalescent plasma transfusion. No adverse events were observed. One possible explanation for the efficacy of convalescent plasma is that the antibodies form convalescent plasma might suppress viraemia.[23]

437) 2020-05-01 C-SPAN: President Trump Oval Office Remarks on Remdesivir. 2020 May 01. https://www.c-span.org/video/?471735-1/president-trump-oval-office-remarks-remdesivir

> Mr. O'Day, Gilead Sciences CEO: What I'd like to say is that, you know, on behalf of Gilead, to the President's point, we feel a tremendous responsibility. We're humbled by this being an important first step for patients, for hospitalized patients. We want to make sure nothing gets in the way of these patients getting the medicine. So we made a decision to donate about 1.5 million vials of remdesivir.

438) 2020-05-01 Sheridan C: Convalescent serum lines up as first-choice treatment for coronavirus. Nature Biotechnology 01 May 2020. https://www.nature.com/articles/d41587-020-00011-1

439) 2020-05-01 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry. https://web.archive.org/web/20200526150255/https://www.fda.gov/media/136798/download

440) 2020-05-01 Pérez-Cameo C, Marín-Lahoz J: Serosurveys and convalescent plasma in COVID-19. EClinicalMedicine 23 (2020) 100370. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7252163/pdf/main.pdf

> The current pandemic is not only overwhelming the health systems of the affected countries but also is killing thousands of other ways healthy adults. Convalescent plasma has been proposed [1] and approved to treat COVID-19 based on the experience acquired treating other viral diseases such as influenza, Ebola, and SARS [2]. It is considered a safe treatment (at least its side effects and contraindications are well known) and it has proven to be efficacious in several viral infections for more than a century. Currently, several countries and health institutions are trying to gather convalescent sera for either empirical treatment or clinical trials. Based on the WHO interim guidance developed for the 2014 Ebola outbreak [3], convalescent plasma has advantages over other proposed treatment: it requires low technology (and therefore it can be produced where required independent of pharmaceutical companies), it is low cost and its production is easily scalable as long as there are sufficient donors.

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441) 2020-05-01 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. (Initial EUA). https://web.archive.org/web/20200501204823/https://www.fda.gov/media/137564/download

Page 2:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

• Distribution of the authorized remdesivir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply remdesivir to authorized distributors[4], or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

• The remdesivir covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO2 ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); ***(The mechanism of remdesivir "…acts as a nucleoside analog and inhibits RNA-dependent RNA polymerase (RdRp) of coronaviruses...".*** Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Hobartner C, Cramer P: Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nature Communicatioins (2021)12:279 https//doi.org/10.1038/s41467-020-20542-0. https://www.nature.com/articles/s41467-020-20542-0.pdf ***Thus, the administration of remdesivir should be given early during the viral replication phase (best in <72 hours from diagnosis) rather than late in the symptomatology of COVID-19 cytokine storm and bradykinin increase.)***

• Remdesivir is administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and

• The use of remdesivir covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

442) 2020-05-01 FDA: Recommendations for Investigational COVID-19 | FDA 1 May 2020: 1-6. http://web.archive.org/web/20200502165610/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

443) 2020-05-01 U.S. Department of Veterans Affairs, VA Pharmacy Benefits Management Services: Remdesivir emergency use authorization (EUA) Requirements, May 2020. https://web.archive.org/web/20201020111539/https://www.va.gov/covidtraining/docs/20200618_Dynamic_Drugs_in_the_Battle_of_COVID_19/Remdesivir_Emergency_Use_Authorization_Requirements.pdf

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INCLUSION CRITERIA ***(The patient must meet all these criteria. All answers must be YES to receive agent).***

Patient is hospitalized with laboratory confirmed COVID-19 diagnosis YES NO

The patient meets at least one of the following: need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), supplemental oxygen, or room air O_2 saturation ≤94% YES NO

Counseling provided and documented in the electronic health record as per EUA ** YES NO

**The provider has communicated with the patient/caregiver information consistent with the "Fact Sheet for Patients and Patients/Caregivers" prior to the patient/caregiver information has been given the Fact sheet, informed that remdesivir is an unapproved drug authorized for use under EUA, given information on alternatives and their risks and benefits, and the patient/caregiver has the right to refuse or accept

444) 2020-05-02 Dowdy D, D'Souza G: Early herd immunity against COVID-19: A dangerous misconception. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/from-our-experts/early-herd-immunity-against-covid-19-a-dangerous-misconception

445) 2020-05-02 U.S. FDA: Fact sheet for health care providers emergency use authorization (EUA) of Remesivir. (GS-5734™) https://web.archive.org/web/20200502180648/https://www.fda.gov/media/137566/download

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

446) 2020-05-02 FDA: Fact Sheet for Health Care Providers Emergency Use AuthoriU.S. Department of Veterans Affairs, Veterans Health Administration. : Remdesivir FAQ https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/FAQ%20SHEETS/Remdesivir%20FAQ%20May%202020%20.docx **No URL has been captured for this domain.**

447) 2020-05-02 Roche JA, Roche R: A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7267506/pdf/FSB2-9999-na.pdf

448) 2020-05-03 Fitzgerald M: Gilead CEO says remdesivir will be available to patients this week: 'We've donated the entire supply.' CNBC 3 May 2020: 1-7. https://www.cnbc.com/2020/05/03/gilead-ceo-says-remdesivir-available-to-coronavirus-patients-this-week-weve-donated-the-entire-supply.html

449) 2020-05-03 Brennan M, O'Day: Transcript: Daniel O'Day discusses coronavirus treatment on "Face the Nation," May 3, 2020. CBS Face the Nation.

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https://www.cbsnews.com/news/transcript-daniel-oday-discusses-coronavirus-treatment-on-face-the-nation-may-3-2020/

MARGARET BRENNAN: Joining us now is Daniel O'Day, chairman and CEO of Gilead Sciences, that's the pharmaceutical company that makes remdesivir. Good morning to you.

GILEAD CEO DANIEL O'DAY: Good morning, MARGARET. Thank you for having me on.

MARGARET BRENNAN: So this drug shaves about four days off the recovery time of someone hospitalized with coronavirus, according to the government study. Now that your company has this emergency use authorization, how quickly will the drug get to those people who need it?

O'DAY: Well, you know, I think I speak on behalf of all of us at Gilead that we are grateful and really humbled that everything has moved so quickly. You know, it's only been three months since the first case was diagnosed in the United States to the emergency use authorization that was provided this past Friday. That's thanks to a lot of patients and caregivers that participated in our clinical trials. And we are now firmly focused on getting this medicine to the- the most urgent patients around the country here in the United States. And, MARGARET, we intend to get that to patients in the early part of this next week, beginning to work with the government, which will determine which cities are most vulnerable and- and where the patients are that need this medicine.

MARGARET BRENNAN: I think that's important. You're saying you've- you've donated some of this drug to the federal government, and you will work with the federal government to decide where the drug goes? Or is that up to the federal government to decide?

O'DAY: Right, MARGARET. So we've donated the entire supply that we have within our supply chain. And we did that because we acknowledge and recognize the human suffering, the human need here and want to make sure that nothing gets in the way of this getting to patients. And what we will do is- is provide that donation to the U.S. government and they will determine, based upon things like ICU beds, where the course of the epidemic is in the United States. They will begin shipping tens of thousands of treatment courses out early this week and be adjusting that as the epidemic shifts and evolves in different parts, in different cities here in the United States.

MARGARET BRENNAN: Okay- okay, well, we have more to talk about with you, but I have to take a quick break here. So stay with us, and stay with us, all of you as well, please. More with Daniel O'Day in a moment.

(COMMERCIAL BREAK)

MARGARET BRENNAN: I want to pick up on this, you said the- the supply of one and a half million doses of remdesivir has been donated to the government. That's enough for what, 150,000 patients or so?

O'DAY: Right, MARGARET. Just to be clear, what we've done is we've donated the entirety of our supply, which is around 1.5 million vials, and that turns into around 100,000 to 200,000 treatment courses depending on whether it's a five-day or a 10-day. And this donation will be made available to patients here in America and the United States and across the world as other regulatory decisions are taken for those countries.

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MARGARET BRENNAN: This drug is clearly going to be in demand since it's the- the first sort of promising development we've had. You were at the White House, has the Trump administration talked to you at all about using the Defense Production Act to somehow mandate that you prioritize the U.S. market over foreign markets?

O'DAY: Yeah, let me say something on the supply and the demand, because, you know, I'm so proud to work with the scientists at Gilead that, you know, that quickly moved and mobilized themselves in January, long before we knew whether the medicine would be available, to increase the supply. This is a long supply process. It used to take around 12 months, and now it takes around six months. And because of the steps we took in January, we'll have significantly more supply in the second half of this year to serve the suffering and the human needs out there. We've been working very closely with the U.S. government and with other governments around the world. In terms of the allocation question, I think we're aligned with the US government to both serve the patients here in the United States and then to be able to also make sure, as a global company based here in the United States, that we can serve other countries around the world as well. We've had very good dialogues with the government and that's going well.

MARGARET BRENNAN: So they haven't talked to you about mandating the U.S. market be prioritized or taking it for the stockpile for example. You can still export it?

O'DAY: That's correct. We have been exporting for clinical trials and for compassionate use, thousands of treatment courses. An- and our collaboration with the government has been such that we've been very transparent with them here in the United States. And we have a good relationship on- on future allocation.

MARGARET BRENNAN: This drug you have to get through an I.V. right now, so it works for hospitalized patients. Will you develop other mechanisms? Does this ever become a pill someone can take at home?

O'DAY: Yes. It's important to note that this medicine is really right now for the most severe patients in the hospital, and it's given by I.V. either through a five-day treatment course or a 10-day treatment course, depending on the stage and nature of the patient. But our scientists have been working since earlier this year to say, are there other ways that we could deliver this medicine, potentially as Dr. Gottlieb mentioned, to earlier patients. And in order to do that, we're looking at formulations such as subcutaneous formulations that may be given outside the hospital setting and possibly an inhaled version. This medicine is not suitable for oral administration because of the way it's metabolized. But there are ways we can look at formulations potentially that would get us to earlier patients and patients outside the hospital setting. That research is still ongoing yet, hasn't yet read out. And we'll certainly keep you up to speed on that.

MARGARET BRENNAN: All right. We will be watching. Thank you very much, Mr. O'Day.

O'DAY: Thank you.

450) 2020-05-05 Siegel E: This is how physics, not math, finally resolved Zeno's famous paradox. Forbes https://www.forbes.com/sites/startswithabang/2020/05/05/this-is-how-physics-not-math-finally-resolves-zenos-famous-paradox/?sh=24f6f51c33f8

451) 2020-05-05 – 2020-09-18: *Historic St. Mary's Mission & Museum est. 1841*: Fr. Pierre Jean De Smet, S.J., 1801-1873. https://www.saintmarysmission.org/fr-desmet

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The Early Montana Missions
Competition for land and resources spurred the Salish to seek what they believed to be the mysterious power of the white man's religion; to gain strength and power over their enemies, the Blackfeet. In the 1830's, the Flathead, Nez Perce and Iroquois tribes sent four delegations to St. Louis in search of Catholic priests, or "Blackrobes". In 1839, they asked Jesuit priest Pierre-Jean De Smet, who three years later followed them back along an ancient trail to the Bitterroot Valley of Western Montana.

The "Blackrobes" established St. Mary's Mission near present-day Stevensville. They taught the native people a belief in Christianity in addition to farming and domestic skills. It was at St. Mary's Mission that Montana's first sawmill was constructed, the first crops were cultivated, and a water-powered gristmill was first put to use.

St. Mary's closed in 1850, and the Jesuit influence expanded with the development of the St. Ignatius Mission. Father De Smet and Father Adrian Hoecken and Joseph Menetrey built several log buildings, including a chapel, two houses, a carpenter's shop and a blacksmith shop. At St. Ignatius, the priority was to establish a mission school to fulfill an educational provision in the Hellgate Treaty of 1855. *–On the wall of the one room chapel of the U.S. Department of Agriculture Museum, Missoula, MT.*

452) 2020-05-06 Li X, Ma X: Acute respiratory failure in COVID-19: is it "typical" ARDS? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202792/pdf/13054_2020_Article_2911.pdf

453) 2020-05-08 Choudhury A, Mukherjee S: In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. JK Me Virol 2020; https://onlinelibrary.wiley.com/doi/10.1002/jmv.25987

454) 2020-05-08 World Health Organization: Commemorating Smallpox Eradication – a legacy of hope, for COVID-19 and other diseases. https://www.who.int/news/item/08-05-2020-commemorating-smallpox-eradication-a-legacy-of-hope-for-covid-19-and-other-diseases

455) 2020-05-10 Pawar AY, Hiray AP, Sonawane DD, Bhambar RS, Derle DV, Ahire YS: Convalescent plasma: A possible treatment protocol for COVID-19 patients suffering from diabetes or underlying liver diseases. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 10 May 2020; 14: 665-669. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7214325/pdf/main.pdf

456) 2020-05-11 Nguyen AA, Habiballah SB, Platt CD, Geha RS, Chou JS. Review Article: Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! Clinical Immunology 2020; 216: 108459. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211658/pdf/main.pdf

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457) 2020-05-11 Aleccia J: Market for blood plasma from COVID-19 survivors heats up. National Public Radio. https://www.npr.org/sections/health-shots/2020/05/11/852354920/market-for-blood-plasma-from-covid-19-survivors-heats-up

458) 2020-05-12 Kesici S, Yavuz S, Bayrakci: Letter: Get rid of the bad first: Therapeutic plasma exchange with convalescent plasma for severe COVID-19. PNAS June 9, 2020; 117 (23) 12526 – 12527. https://www.pnas.org/content/pnas/117/23/12526.full.pdf

459) 2020-05-12 Zeng F, Chen X, Deng G: Letter: Convalescent plasma for patients with COVID-19. PNAS June 9, 2020; 117 (23): 12528. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7293648/pdf/pnas.202006961.pdf

460) 2020-05-12 U.S. Food and Drug Administration, HHS: Guidance documents related to coronavirus disease 2019 (COVID-19); Availability. https://www.federalregister.gov/documents/2020/05/12/2020-10146/guidance-documents-related-to-coronavirus-disease-2019-covid-19-availability and *specific entry into the Federal Register*: Department of Health and Human Services, Food and Drug Administration: [Docket Nos. FDA-2020-D-1106, FDA-2020-D-1137, FDA-2020-D-1138, FDA-2020-D-1139, and FDA-2020-D-1140]: Guidance documents related to coronavirus disease 2019 (COVID-19); Availability. Federal Register Volume 85, Number 92 (Tuesday, May 12, 2020), [Notices], [Pages 28010-28016] from the Federal Register Online via the Government Publishing Office [www.gpo.gov], [FR Doc No: 2020-10146] https://www.govinfo.gov/content/pkg/FR-2020-05-12/html/2020-10146.htm

461) 2020-05-13 Datta SS, Basu ES: Randomization amid a pandemic – critical appraisal regarding convalescent plasma therapy clinical trials for COVID-19 patients. International Society of Blood Transfusion, ISBT Science Series 2020; 0: 1-2. https://onlinelibrary.wiley.com/doi/full/10.1111/voxs.12564

462) 2020-05-13 Roos D: How crude smallpox inoculations helped George Washington win the War – As commander of the Continental Army, Washington faced dual enemies: The British and smallpox. So he made a risky move. History Channel. https://www.history.com/news/smallpox-george-washington-revolutionary-war

a. But immunization in the 1770s was not what it's like today with a single injection and a low risk of mild symptoms. Edward Jenner didn't even develop his revolutionary cowpox-based vaccine for smallpox until 1796. The best inoculation technique at Washington's disposal during the Revolutionary War was a nasty and sometimes fatal method called "variolation."

b. "An inoculation doctor would cut an incision in the flesh of the person being inoculated and implant a thread laced with live pustular matter into the wound," explains Fenn. "The hope and intent was for the person to come down with smallpox.

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When smallpox was conveyed in that fashion, it was usually a milder case than it was when it was contracted in the natural way."

c. Variolization still had a case fatality rate of 5 to 10 percent. And even if all went well, inoculated patients still needed a month to recover. The procedure was not only risky for the individual patient, but for the surrounding population. An inoculee with a mild case might feel well enough to walk around town, infecting countless others with potentially more serious infections.

463) 2020-05-14 Anderson J, Schauer J, Bryant S, Graves CR: The use of convalescent plasma therapy and Remdesivir is the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report. Case Reports in Women's Health (2020), https://doi.org/10.1016/j.crwh.2020.e00221. https://www.sciencedirect.com/science/article/pii/S2214911220300515?via%3Dihub

464) 2020-05-14 Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Buskirk CMV, Winters JL, Stubbs JR, Paneth NS, Casadevall A: Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. MedRxiv – Preprint May 12, 2020. https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1.full.pdf

465) 2020-05-14 Epstein J, Burnout T: Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. Vox Sanguinis (2020) 115: 485-487. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7264781/pdf/VOX-9999-na.pdf

466) 2020-05-14 Dhochak N, Singhal T, Kabra SK, Lodha: Pathophysiology of COVID-19: Why children fare better than adults? Indian J Pediatrics. (published online on May 14, 2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7221011/pdf/12098_2020_Article_3322.pdf

467) 2020-05-16 Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye Y, Liu B, Yang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zan Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C: Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial. The Lancet 16 May 2020; 395: 1569-1578. https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31022-9.pdf

468) 2020-05-16 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. May 1, 2020. https://web.archive.org/web/20200818023056/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

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469) 2020-05-18 Peng F, Tu L, Yan Y, Hu P, Wang R, Hu Q, Cao F, Jiang T, Sun J, Xu G, Chang C: Review Management and Treatment of COVID-19: The Chinese Experience. Canadian J Cardiology 2020 Jun; 36(6): 915-930. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7162773/pdf/main.pdf

470) 2020-05-18 Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y, Zhang S: Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest 2020 Jul; 158(1):e9-e13. Doi: 10.1016/j.chest.2020.03.039. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7195335/pdf/main.pdf

471) 2020-05-21 Sahu KK, Jindal V, Siddiqui AD, Cerny J, Gerber JM: Convalescent plasma therapy: A passive therapy for an aggressive COVID-19. J Med Virology 2020; 92: 2251-2253. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.26047

472) 2020-05-22 Accorsi P, Berti P, de Angelis V, De Silvestro G, Mascaretti L, Ostuni A, on behalf of the Italian Society for Haemapheresis and Cell Manipulation (SIdEM): Position paper on the preparation of immune plasma to be used in the treatment of patients with COVID-19. Blood Transfusion 2020 May; 18(3): 163-166. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250681/pdf/blt-18-163.pdf

473) 2020-05-26 U.S. Food and Drug Administration: Guidance Document: Investigational COVID-19 convalescent plasma—*Guidance for* Industry, May 2020: 1-2. http://web.archive.org/web/20200614144608/https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research: Investigational COVID-19 convalescent plasma – Guidance for Industry. April 2020, Updated May 1, 2020: 1-8. http://web.archive.org/web/20200526150255/https://www.fda.gov/media/136798/download ; Federal Register, Volume 85 Issue 101 (Tuesday, May 26, 2020) https://www.govinfo.gov/content/pkg/FR-2020-05-26/html/2020-11238.htm

474) 2020-05-28 Zhu M, Hu K, Zhu Z: Letter to the Editor: Use of convalescent plasma in COVID-19 patients in China. Published online 2020 May 16. Tranfus Clin Biol 2020 Aug; 27(3): 168-169. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7228875/pdf/main.pdf

475) 2020-05-28 Epstein J, Smid M, Wendel S, Somuah D, Burnout T: Use of Covid-19 Convalescent plasma in low-and middle-income countries: a call for ethical principles and the assurance of quality and safety. https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7283681&blobtype=pdf Published as a commentary in VoxSanguinis (2021) 116, 13-14. https://onlinelibrary.wiley.com/doi/epdf/10.1111/vox.12964

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> …The curative effect of convalescent plasma is closely related to the quality, dose, antibody titer and infusion time of the plasma. …

476) 2020-05-30 Alsuliman T, Alasadi L, Alkharat B, Srour M, Alrstom A: A review of potential treatments to date in COVID-19 patients according to the stage of the disease. Current Research in Translational Medicine 68 (2020) 93 – 104. https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7260520&blobtype=pdf

> Convalescent plasma The FDA has recently approved convalescent plasma for serious or immediately life-threatening COVID-19 infections under emergency Investigational New Drug Application (eINDs) [80]. Convalescent plasma has been previously studied during other epidemics including H1N1 influenza virus pandemic, SARS-CoV-1 epidemic, and the MERS-CoV epidemic. Recently, a preliminary case series of five intubated COVID-19 patients with ARDS showed promising results. These patients received 400 ml of convalescent plasma containing neutralizing SARS-CoV-2–specific antibody (IgG) from recovered COVID-19 donors. All patients had gradual clinical and radiological improvement within 3 days and four patients no longer required respiratory support by day 9, viral loads also became negative within 12 days after transfusion. Seven clinical trials are currently registered [7,38,81].

477) 2020-06 Yuki K, Miho F, Koutsogiannaki S: COVID-19 pathophysiology: a review. Clinical Immunology 2020 June; 215 (2020) 108427. https://www.sciencedirect.com/science/article/abs/pii/S152166162030262X https://reader.elsevier.com/reader/sd/pii/S152166162030262X?token=41F038E37E30DFE2815B6F320E62962A19EF9BEB41D928112EC631409FFAE7AAACA4DE6C9893CC0A7A5E2066E32579C4&originRegion=us-east-1&originCreation=20220111220308

478) 2020-06-02 Marson P, Cozza A, De Silvestro G: Letter to the Editor: The true historical origin of convalescent plasma therapy. Transfusion and Apheresis Science 2020; 59 (102847) https://www.thepharmaletter.com/article/hhs-and-regeneron-collaborate-to-develop-2019-ncov-treatment

479) 2020-06-02 or 2020-06-06 The pharma letter: HHS and Regeneron collaborate to develop 2019-nCoV treatment. https://www.thepharmaletter.com/article/hhs-and-regeneron-collaborate-to-develop-2019-ncov-treatment ***(Unfortunately, while this was accessed 3/18/2021, today—05-22-2021—the following can only be accessed by subscription)***

> To develop therapeutics to treat the 2019 novel coronavirus, the US Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) will expand an existing collaboration with US biotech Regeneron Pharmaceuticals (Nasdaq: REGN), whose shares rose 4.5% to $372.16 on the news yesterday.
>
> "Emerging infectious diseases can present serious threats to our nation's health security," said Rick Bright, deputy assistant secretary for preparedness and response and director of the Biomedical Advanced Research and Development Authority (BARDA) at ASPR, adding: "Working as public-private partners like we have with Regeneron since 2014, we can move rapidly to respond to new global health threats."
>
> "The life-saving results seen with our investigational Ebola therapy last year underscore the potential impact of Regeneron's rapid response platform for addressing emerging outbreaks," said Dr George Yancopoulos, president and chief scientific officer of Regeneron. "Our unique suite of technologies expedites and improves the drug discovery and development process at every

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stage, positioning Regeneron to respond quickly and effectively to new pathogens. We are eager to expand our productive collaboration with BARDA and are already working hard to address the novel coronavirus that is causing worldwide concern," he noted.

The BARDA and Regeneron now will leverage their partnership agreement to develop multiple monoclonal antibodies that, individually or in combination, could be used to treat this emerging coronavirus, also known as 2019-nCoV.

Will leverage Regeneron's VelocImmune platform

Medicines developed for 2019-nCoV through the expanded BARDA-Regeneron partnership will leverage Regeneron's monoclonal antibody discovery platform called VelocImmune, part of the company's VelociSuite technology.

In addition to expanded collaboration with Regeneron, BARDA is working with counterparts across the government, including within HHS and with the Department of Defense. The team is reviewing potential vaccines, treatments and diagnostics from across the public and private sectors, particularly products in development for MERS or Severe Acute Respiratory Syndrome (SARS), to identify promising candidates for development to detect, protect against or treat 2019 nCoV.

480) 2020-06-02 European Blood Alliance: Convalescent Plasma. https://web.archive.org/web/20200603052709/https://europeanbloodalliance.eu/activities/convalescent-plasma-cpp/

481) 2020-06-02 European Blood Alliance: Convalescent plasma (CCP). What is COVID-19 Convalescent Plasma (CCP). https://europeanbloodalliance.eu/activities/convalescent-plasma-cpp/

482) 2020-06-02 Rubin R: Testing an old therapy against a new disease: Convalescent Plasma for COVID-19. https://jamanetwork.com/journals/jama/fullarticle/2765617

483) 2020-06-03 Humeniuk R, Mathias A, Cao H, Osinusi A, Shen G, Chng E, Ling J, Vu A, German P: Safety, tolerability, and pharmacokinetics of Remdesivir, An antiviral for treatment of COVID-19, in healthy subjects. Clin Transl Sci 2020; 13: 896 - 906. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361781/pdf/CTS-13-896.pdf

484) 2020-06-03 Casadevail A, Joyner MJ, Pirosfki LA: A randomized trial of convalescent plasma for COVID-19 -- Potentially hopeful signals. JAMA. June 3, 2020: E1 – E3. https://pubmed.ncbi.nlm.nih.gov/32492105/ ; August 4, 2020; 324 (5): 455-457. https://jamanetwork.com/journals/jama/fullarticle/2766940

485) 2020-06-05 Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, Yu Z, Zhang W, Zhong Q, Zheng X, Sang L, Jiang L, Zhang J, Xiong W, Liu J, Chen D: Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. Annals of Intensive Care 05 Jun 2020; 10(1): 73 to ~97. https://europepmc.org/article/med/32506258

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Statement 8 Convalescent plasma therapy should probably be used for severe and critically ill patients with COVID-19 (Grade 2+, weak recommendation).

Rationle Convalescent plasma has been testified to suppress viremia, shorten the hospital stay, and reduce mortality during several virus epidemics. …

…regardless of these limitations, since there are still no specific etiological treatments for COVID-19, and convalescent plasma is available, it is reasonable to use it in the treatment of COVID-19 patients.

486) 2020-06-08 Abbasi J: Anthony Fauci, MD, on COVID-19, Schools, and Larry Kramer. JAMA.com. JAMA 2020;324(3): 220-222 https://jamanetwork.com/journals/jama/fullarticle/2767208

Dr. FAUCI: Right now we have a major push on a program to develop monoclonal antibodies, convalescent plasma, and hyperimmune globulin, all of which are founded on the same principle of using an antibody that is directed against the virus for either prophylaxis or treatment. And I think you're going to see it's going to be both. We'd like to have available for those who are at risk—elderly and those with underlying conditions—either monoclonal antibodies or convalescent plasma. That's a very, very high priority.

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Dr Bauchner: Your equanimity, does it come from your parents? Does it come from your Jesuit education? It's extraordinary under the face of remarkable criticism, almost always unfair.

Dr Fauci:I think it does come a lot from my parents. My father was very much of a tolerant person who would accept people for what they are and very rarely ever criticized anybody. I went to a Jesuit high school in Manhattan, and from there I went to a Jesuit college. I think it was just right for me because I had always been interested in public service and not being somebody that ever attacks anybody, that accepts them for who they are and what they are. So it was kind of the perfect atmosphere to me to be educated in, and I just carried it along with me.

Feuerherd P: Dr. Fauci is dedicated to public service, formed at Jesuit high school. Catholic Review—Inspiring the Archdiocese of Baltimore. 2020 March 30. https://catholicreview.org/dr-fauci-is-dedicated-to-public-service-formed-at-jesuit-high-school/

487) 2020-06-08 Andrus CH: Time: The Crucial Independent Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029. https://web.archive.org/web/20210904014401/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=9&ti=1%2C9&Search_Arg=Andrus+Charles+H&Search_Code=NALL&CNT=25&PID=DvTGOW_Qvd_foYxTFrVcdewL3ktMCwz&SEQ=20210425193720&SID=1

488) 2020-06-08 Chen J, Lu H, Melino G, Boccia S, Placentini M, Ricciardi W, Wang Y, Shi Y, Zhu T: COVID-19 infection: The China and Italy perspectives. Cell Death and Disease (2020)11 (6):438 (pages 1 – 17). https://www.nature.com/articles/s41419-020-2603-0.pdf

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Page 12 of 17:
Convalescent plasma

Convalescent plasma is also a potentially promising strategy to treat COVID-19. In a recent case study, the clinical status of all the five critically ill COVID-19 patients receiving convalescent plasma showed a significant improvement within 1 week following the infusion, normalization of body temperature, as well as scores of the sequential organ failure assessment. Moreover, within 1-12 days following the infusion, the neutralizing antibody titers of the patients improved and the respiratory samples tested negative fokr SARS-CoV-2 (ref. [62]). In another study of 10 severe cases, the viral titers were undetectable following the infusion in seven patients who had previously high viremia[63]. Previous studies on other respiratory viral diseases provided some evidences on the efficacy of convalescent plasma on treating severe and critical viral diseases. Several studies in SARS patients reported that the use of convalescent plasma was linked to reduced hospital stay and reduced mortality[64,65]. Clinical trials also showed that in patients with severe H1N1 influenza A, in the 2009 pandemic, therapy with convalescent plasma from patients who recovered, especially within 5 days of symptom onset, resulted in a lower viral load and lower mortality[66,67]. Subsequent analysis showed that the mortality of patients with severe acute viral respiratory infections was reduced after therapy with convalescent plasma, while absence of adverse events or complications were observed[68].

Nevertheless, there are still issues we need to tackle. The first question is when to collect plasma from recovered COVID-19 patients. Recent work by To et al.[25] showed that, day 10 after symptom onset, both IgG and IgM antibodies increased in the majority of patients, while seroconversion was observed with the first 3 weeks. Importantly, the anti-SARS-CoV-2 IgG and IgM antibody levels against the internal nucleoprotein and the spike S1 domain correlated with neutralizing activity. Therefore, it would be ideally to collect convalescent plasma from week 3 after symptom onset. Despite hundreds of patients had recovered from COVID-19, eligible convalescent plasma is quite limited as the donors have to pass physical and laboratory examination, and plasma should be tested for SARS-CoV-2 nuclear acid, HIV-1, HBV, and HCV, as well as antibody titers, to list a few. The second question is deciding which patients and when should receive the convalescent plasma. The effects of convalescent plasma are difficult to observed when used in critical patients with multiple organ failure, as the viral load in this kind of population is quite high. Hence it is preferably to use convalescent plasma in mild patients whose diseases was deteriorating in their early phase of diseases. Normally, in COVID-19, the viral load peaked at the first week of illness, and then slowly decline during the subsequent seek[25]. Accordingly, in principle, the most effective to administer the convalescent plasma is at the early phases of the disease. The biggest challenge is that it is quite difficult to identify which patient will deteriorate in the early stage. Several risk factors including older age, male, multiple comorbidities, elevated IL-6, and elevation in D-dimer levels that are associated with bad outcomes may be used as surrogate markers[10]. Provided further studies demonstrate its efficacy in appropriately selected patients, the next step would be the production of humanized antibody at biotechnological level.

489) 2020-06-10 Yigenoglu TN, Hacibekiroglu T, Berber I, Dal MS, Basturk A, Namdaroglu S, Korkmaz S, Ulas T, Dal T, Erkurt MA, Turgut B, Altuntas F: CONCISE REVIEW Convalescent plasma therapy in patients with COVID-19. J Clin Apher 2020; 35: 367-373. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jca.21806

490) 2020-06-10 **Harris KM: Letter at the request of Dr. Fauci designating NIAID Case# 12276.** 06 Appendices A-H copy; Appendix G—NIH and FDA responses including the establishment NIAID #12276 6-10-2020; NIH and FDA responses including 6-6-

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2020 re NIAID Case #12276.pdf **ANY Person under the Freedom of Information Act (FOIA) can request NIAID Case #12276—see reference 206 in this bibliography:**

While the website above the generalities, to submit FOIA request is somewhat complicated and the following disclaimer for the NIH—National Institutes of Health in part is: …Please submit all requests through our online portal (link below) rather than mail, fax, or courier, to ensure timely logging of your requests….

First (1): https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/freedom-information-act-office/submitting-foia-requests

Next (2): click on the Submit a FOIA Request:

Next (3): The following disclaimer will show up which after reading it, if one wishes to proceed, you should click on "I Accept":

491) 2020-06-11: Stankiewicz K: Regeneron sees 'a lot of reason for hope' as human testing of its coronavirus drug begins. CNBC. https://www.cnbc.com/2020/06/11/regeneron-begins-human-testing-of-its-coronavirus-antibody-drug.html

KEY POINTS

- Regeneron Pharmaceuticals announced Thursday that it's started the first clinical trial of its experimental coronavirus antibody drug.
- The antibody cocktail is being tested in four human populations, with two groups of people receiving the drug as a treatment and two as a possible prevention.
- "I think there's a lot of reason for hope," Regeneron's chief scientific officer, Dr. George Yancopoulos, said on CNBC's "Squawk Box."

- Regeneron Pharmaceuticals announced Thursday that it's started the first clinical trial of its experimental coronavirus antibody drug.
- The antibody cocktail is being tested in four human populations. Two groups of people will receive the drug to test its effectiveness as a treatment for Covid-19; the other two will receive it as a possible prevention.
- "We'll be hopefully to quickly test the safety and then start understanding the efficacy for four major different settings of this virus challenge," Regeneron's chief scientific officer, Dr. George Yancopoulos, said on CNBC's "Squawk Box."

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- Yancopoulos said he thinks that, "if all goes well," the company could have "definitive data" within a few months on the effectiveness of the antibody cocktail.
- "I think there's a lot of reason for hope," Yancopoulos said, noting the company's work on Ebola. But he also stressed the unpredictable nature of science and biology, saying "there's always reasons to be concerned and to be cautious."
- "So we're going to be moving forward very carefully, hand-in-hand in with the FDA, and we hope sooner rather than later we can get answers that can really make a difference," he said.
- Regeneron is the latest company to begin trials for a potential Covid-19 therapy. Eli Lilly, which began trials of its antibody drug earlier this month, said a treatment could be authorized, if all goes well, for use as early as September. In scientific trials so far, Gilead Sciences's antiviral remdesivir is the only drug to show some effectiveness in treating the disease.
- There are more than 7.4 million confirmed cases of Covid-19 in the world, including over 2 million in the U.S., according to the latest data from Johns Hopkins University. More than 417,100 people have died worldwide, with over a quarter of the fatalities in the U.S.
- Regeneron's drug is being tested on four distinct types of patients, including "the sickest patients" who are hospitalized and on a ventilator or oxygen support, Yancopoulos said. It's also being tested to see whether it can prevent high-risk people from contracting the disease, such as health-care workers.
- The drug, known as REGN-COV2, is a combination of two antibodies. Yancopoulos said Regeneron firmly believes this is the correct approach to treat Covid-19 when using antibodies.
- "Just like with conventional, old fashion antiviral drugs, giving one can have enormous benefit initially but it can lead to the selection and the arise of escaped viral mutants, which can could be very dangerous and risky," he said. "What we showed is that in order to prevent this, you have to give these antibodies in cocktails."

492) 2020-06-15 Marovich M, Mascola JR, Cohen MS: Monoclonal antibodies for prevention and treatment of COVID-19. JAMA 2020 June 15; 324: 131-132. https://jamanetwork.com/journals/jama/fullarticle/2767383

The coronavirus disease 2019 (COVID-19) pandemic has created a worldwide crisis and inspired an urgent search for prevention and treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Attention has focused on the development of vaccines, new antiviral agents, and convalescent plasma infusions. Monoclonal antibodies have received less attention even though neutralizing antibodies are a key component of protective immunity for most viral diseases. Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential for both therapeutic and prophylactic applications, and can help to guide vaccine design and development.1 ….

Conclusions

Neutralizing antibodies have an important role in the protection or recovery from many viral infections. Several monoclonal antibody products will enter clinical trials over the next few months and be assessed for their ability to limit or modify SARS-CoV-2 infection. In addition, a drug that reliably prevented progression of COVID-19 would greatly reduce the concerns and uncertainty associated with SARS-CoV-2 infection and give physicians a therapeutic tool they

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must have for their patients. Establishing the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major advance in the control of the COVID-19 pandemic.

493) 2020-06-15 FDA: Coronavirus (COVID-19) Update: FDA revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and

494) 2020-06-18 Mahant V: "Right-to-Try" experimental drugs: an overview. J Transl Med 2020; 18: 253-263. NCBI published version: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7309195/ Pdf published version: https://translational-medicine.biomedcentral.com/track/pdf/10.1186/s12967-020-02427-4.pdf

In May 2018, President Donald Trump signed the "Right-to-Try" Act [5]. The legislation overcame many of the regulatory barriers, limited the risks to the sponsor while implementation of the act inherently burdened the sponsor. The "Right-to-Try" legislation is in essence a derivative of the Expanded Access Programs (EAPs). Advocates such as patients, families, friends and advocacy groups of the "Right-to-Try" legislation argue that the legislation is in line within the pre-existing framework of EAPs and that the legislation: (i) provides a "streamlined" avenue for making eligible drugs available to eligible patients with no other options; (ii) it increases patient's engagement; (iii) it is a patient's journey of self-actualization; (iv) it empowers the patient about his or her own health, well-being and quality of life; (v) it provides optimism and access to novel interventions with potential therapeutic benefits that may prolong life and improve quality of life; and (vi) the patient can be treated in the USA with valuable family time, more comfort and fewer risks than being treated overseas. The critics, on the other hand, argue: (i) there is an inherent safety risk that may potentially cause more harm to the patient or even death than the benefit because the experimental drug did not undergo rigorous testing; (ii) there is a lack of oversight by the FDA, except posting of the consolidated annual summary report; (iii) the patient in most cases has limited understanding of the informed consent due to complexity and confusion of the medical terminology used in the consent form; (iv) there are therapeutic misconceptions combined with high expectations and optimism by the patient; (v) there is potentially a considerable financial burden by the patient or the patient's family because payors currently do not provide coverage and deny hospice care; (vi) there is a potential loss of trust in the regulatory agency, the sponsor and the health care provider; and (vii) there is a liability "immunity" for the health-care provider, including the drug sponsor for potential negative outcomes of the treatment unless the medical provider and the sponsor were engaged in "gross negligence, reckless or "wilful misconduct." …

The implications of ethics, law, regulations, government policies, constitutional rights by terminal ill patients, patient advocacy groups, including stakeholders about the pros and cons echoed through the "ecosystem" of early access to investigational drugs. Under the "Right-to-Try" legislation, the eligibility to participate include: (i) the patient must have been diagnosed with a debilitating or life-threatening disease; (ii) the patient must have failed all standard of care treatments; **(iii) the experimental or the investigational drug must have completed at least phase 1 trial;** (iv) the patient must have signed an informed consent [6]; and (vi) the pharmaceutical company must be able to provide the experimental drug to the patient. Due to the potentially negative outcome about the therapeutic efficacy combined with the safety issues, most sponsors developing medications for life-threatening diseases have had reservations about participating in expanded access or the "Right-to-Try" programs. To de-risk the potential negative outcomes and the implications combined with an opportunity to target a much larger number of patients than to a few eligible patients under the

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early access programs, the sponsors' primary goal --has been to have full FDA approval of the drug. The drug approval process, of course, is lengthy and highly risky due to potential clinical trial failures along each step of the approval process. It is an expensive process—currently, estimated to be between US$ 1.9–2.5 billion [7, 8]. …

Conclusion
The progress made on several fronts in healthcare and the concerted efforts by the stakeholders, including the integral role of agencies such as World Health Organization (WHO) and Global Health Council (GHC) over the last few decades for the treatment of diseases, patient and public engagements, the role of healthcare practitioners, the role of education, data ownership, data sharing, transparency, privacy, ethics, standardization across the multi-industries, regulations, compliance, funding of programs, payment by medical insurance companies, including global policy development and implementation currently present limited opportunities and many challenges for the "Right-to-Try" experimental drugs for the treatment of life-threatening diseases. The "Right-to-Try" experimental drug is nevertheless a major "milestone" along the journey and its full impact on treating life-threatening diseases such as cancer and infectious diseases such as COVID-19 remain to be seen. One of the biggest impacts of emergency use of experimental drugs and compassionate drugs or "repurposing" of drugs is unfolding during the current coronavirus pandemic crisis.

495) 2020-06-19 McEnany K: White House Press Conference, June 19, 2020. https://www.youtube.com/watch?v=GxX6CgI7RJ4

…Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging…

496) 2020-06-20 KPIX 5, CBS SF, BayArea: Photos: Juneteenth Protester Topple Golden Park Statues of Serra, Key, Grant. https://sanfrancisco.cbslocal.com/2020/06/20/juneteenth-protesters-topple-golden-gate-park-statues-of-junipero-serra-francis-scott-key-u-s-grant/

497) 2020-06-20 Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Chen Z, Zhang X, Yang X: Reply to Kesici et al. and Zeng et al.: Blocking the virus and reducing the

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inflammatory damage in COVID-19. Proceedings of the National Academy of Sciences. https://www.pnas.org/content/117/23/12529

> First of all, this study was a pilot trial and the aim was to investigate the safety of CP transfusion, which was defined as the primary endpoint (3). We nevertheless also explored the possible therapeutic benefits of CP by examining its effectiveness in neutralizing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in ameliorating clinical symptoms and paraclinical criteria in recipients. Indeed, the adverse effect was minor, whereas a quickly improved outcome of 10 severe COVID-19 patients was observed. There are of course a number of issues to be addressed, such as the confirmation of the clinical effectiveness in a phase II controlled, randomized trial.
>
> Second, the objective for CP transfusion in severe COVID-19 therapy is based on an in-depth understanding of disease mechanisms. The pathogenesis of this epidemic involves the interaction between viral replication of SARS-CoV-2 and human immune response (4). Particularly, in severe or critical COVID-19 cases, lung alveolar macrophages or epithelial cells could produce various proinflammatory cytokines and chemokines, which recruit monocytes and neutrophils to the infection site to clear the virus particles and infected cells, resulting in uncontrolled inflammation. The uncontrolled virus infection leads to more macrophage infiltration and a further worsening of lung injury. Therefore, the key point of CP therapy is to neutralize the virus and to interrupt the vicious cycle of excessive activation of the immune response in severe patients. In our study, 200 mL CP containing neutralized antibody above 1:640 rapidly cleared the viremia and achieved clinical improvement. Considering the accessibility of plasma donors, using CP as replacement fluid for the therapeutic plasma exchange may be not feasible.
>
> Third, the optimal treatment time and dose of CP need to be determined by the knowledge on viral proliferative kinetics. Zhou et al. (5) reported that the median viral shedding time was 20.0 d in survival patients. Huang et al. (6) observed that the viral load gradually decreased in the respiratory tract after 7 d of illness onset but can be detected after 28 d of illness onset in two-thirds of critically ill patients. Chen et al. (7) found the serum viremia was detected in 29.4% (5/17) critically ill patients and was significantly correlated with the level of interleukin-6. Thus, monitoring the dynamic changes of interleukin-6 level, which was significantly elevated in COVID-19, may help to determine the optimal treatment time, generally within 2 wk.
>
> Finally, the optimal time for collecting CP should be determined by the time and level of total antibody production in convalescent patients. The presence of antibodies was <40% among patients within 1 wk since onset and rapidly increased to 100.0% (antibody), 94.3% (immunoglobulin M), and 79.8% (immunoglobulin G [IgG]) since day 15 after onset (8). Also, the neutralizing antibody titer was correlated with the IgG antibodies (9). The median duration of hospitalization for COVID-19 patients was 12.0 d (**10**). In our study, all of the donors were recovered from the common type of COVID-19. Therefore, the collection of CP from the convalescent patients may be 3 wk after the illness onset, and routine inactivation of plasma should be performed for elimination of potential existing virus. The optimal dose of CP can be calculated based on an empirical formula: volume (liters) = weight of the recipient (kilograms) × the antibody titer of CP

498) 2020-06-22 Hurd D, Smith C, Quintana S: Demonstrators topple statues in San Francisco's Golden Gate Park. NBC BAY AREA.

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https://www.nbcbayarea.com/news/local/san-francisco/demonstrators-topple-statues-in-san-franciscos-golden-gate-park/2312839/

499) 2020-06-23 U.S. Department of Health and Human Services: Testimony from Anthony S. Fauci, M.D. on Oversight of the Trump Administration's Response to the COVID-19 Pandemic Before House Committee on Energy and Commerce, June 23, 2020. https://republicans-energycommerce.house.gov/hearings/oversight-of-the-trump-administrations-response-to-the-covid-19-pandemichybrid-hearing/

500) 2020-06-26: Krejci C, Davis E: Banner Health, Dignity Health activate surge plans as COVDI-19 hospitalizations grow. Azcentral https://www.azcentral.com/story/news/local/arizona-health/2020/06/26/banner-health-activates-surge-plans-increase-covid-19-hospitalizations-capacity/3266635001/

501) 2020-06-23 U.S. FDA: Testimony on Oversight of the Trump Administration's Response to the COVID-19 Pandemic Before House Committee on Energy and Commerce, June 23, 2020. https://www.fda.gov/news-events/congressional-testimony/oversight-trump-administrations-response-covid-19-pandemic-06232020

502) 2020-06-28 Stracqualusi V: 'Window is closing' for US to get coronavirus under control, Trump's HHS secretary warns. CNNpolitics, Jun 28, 2020. https://www.cnn.com/2020/06/28/politics/hhs-alex-azar-coronavirus-rise-in-cases-cnntv/index.html

503) 2020-06-28 Tapper J: Trump pushes to dismantle Obamacare during pandemic. https://www.cnn.com/videos/politics/2020/06/28/sotu-obamacare-lawsuit.cnn

504) 2020-06-29 Steinbach A, Innes S, Leingang R: Arizona hospitals can start activating 'crisis care' standards due to COVID-19 surge. azcentral. https://www.azcentral.com/story/news/local/arizona-health/2020/06/29/arizona-leaders-doctors-crisis-care-standards-coronavirus/3280852001/

505) 2020-07-03 Duda J: As COVID-19 worsens, AZ is the first state to enact 'crisis care' standards. Arizona Mirror. https://www.azmirror.com/2020/07/03/as-covid-19-worsens-az-is-the-first-state-to-enact-crisis-care-standards/

506) 2020-07-06 Arnold C: Convalescent plasma: A COVID-19 treatment speeds to clinical trials. https://magazine.jhsph.edu/2020/convalescent-plasma-covid-19-treatment-speeds-clinical-trials

507) 2020-07-07 Garvin MR, Alvarez C, Izaak Miller J, Prates ET, Walker AM, Kirtley Amos B, Justice A, Aronow B, Jacobson D: A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. eLife, Jul 7, 2020; 1-16 pages. https://elifesciences.org/articles/59177 Copied *verbatim* are from pertinent sections of this

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very important article on the pathophysioiology of the inflammatory storm which is relatively (>8 days) late component of COVID-19 pathologic symptomatology versus the earlier viremic phase (0 to ~8 days).

Abstract

Neither the disease mechanism nor treatments for COVID-19 are currently known. Here, we present a novel molecular mechanism for COVID-19 that provides therapeutic intervention points that can be addressed with existing FDA-approved pharmaceuticals. The entry point for the virus is ACE2, which is a component of the counteracting hypotensive axis of RAS. Bradykinin is a potent part of the vasopressor system that induces hypotension and vasodilation and is degraded by ACE and enhanced by the angiotensin1-9 produced by ACE2. Here, we perform a new analysis on gene expression data from cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients that were used to sequence the virus. Comparison with BALF from controls identifies a critical imbalance in RAS represented by decreased expression of ACE in combination with increases in ACE2, renin, angiotensin, key RAS receptors, kinogen and many kallikrein enzymes that activate it, and both bradykinin receptors. This very atypical pattern of the RAS is predicted to elevate bradykinin levels in multiple tissues and systems that will likely cause increases in vascular dilation, vascular permeability and hypotension. These bradykinin-driven outcomes explain many of the symptoms being observed in COVID-19.

eLife digest

In late 2019, a new virus named SARS-CoV-2, which causes a disease in humans called COVID-19, emerged in China and quickly spread around the world. Many individuals infected with the virus develop only mild, symptoms including a cough, high temperature and loss of sense of smell; while others may develop no symptoms at all. However, some individuals develop much more severe, life-threatening symptoms affecting the lungs and other parts of the body including the heart and brain.

SARS-CoV-2 uses a human enzyme called ACE2 like a ‘Trojan Horse’ to sneak into the cells of its host. ACE2 lowers blood pressure in the human body and works against another enzyme known as ACE (which has the opposite effect). Therefore, the body has to balance the levels of ACE and ACE2 to maintain a normal blood pressure. It remains unclear whether SARS-CoV-2 affects how ACE2 and ACE work.

When COVID-19 first emerged, a team of researchers in China studied fluid and cells collected from the lungs of patients to help them identify the SARS-CoV-2 virus. Here, Garvin et al. analyzed the data collected in the previous work to investigate whether changes in how the body regulates blood pressure may contribute to the life-threatening symptoms of COVID-19.

The analyses found that SARS-CoV-2 caused the levels of ACE in the lung cells to decrease, while the levels of ACE2 increased. This in turn increased the levels of a molecule known as bradykinin in the cells (referred to as a ‘Bradykinin Storm’). .Previous studies have shown that bradykinin induces pain and causes blood vessels to expand and become leaky which will lead to swelling and inflammation of the surrounding tissue. In addition, the analyses found that production of a substance called hyaluronic acid was increased and the enzymes that could degrade it greatly decreased. Hyaluronic acid can absorb more than 1,000 times its own weight in water to form a hydrogel. The Bradykinin-Storm-induced leakage of fluid into the lungs combined with the excess hyaluronic acid would likely result in a Jello-like substance that is preventing oxygen uptake and carbon dioxide release in the lungs of severely affected COVID-19 patients.

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Therefore, the findings of Garvin et al. suggest that the Bradykinin Storm may be responsible for the more severe symptoms of COVID-19.

Further experiments identified several existing medicinal drugs that have the potential to be re-purposed to treat the Bradykinin Storm. A possible next step would be to carry out clinical trials to assess how effective these drugs are in treating patients with COVID-19. In addition, understanding how SARS-Cov-2 affects the body will help researchers and clinicians identify individuals who are most at risk of developing life-threatening symptoms.

Introduction

The COVID-19 beta-coronavirus epidemic that originated in Wuhan, China in December of 2019 is now a global pandemic and is having devastating societal and economic impacts. The increasing frequency of the emergence of zoonotic viruses such as Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) (among others) are of grave concern because of their high mortality rate (10%–90%). Fortunately, successful containment of those pathogens prevented global-scale deaths. In contrast, the current estimates of mortality for COVID-19 are much lower (~4%), but the virus has now infected more than nine million people and caused nearly a half a million deaths. The cause of mortality appears to be heterogeneous and although it typically targets older individuals, younger individuals are also at risk. A key to combating the pandemic is to understand the molecular basis of COVID-19 that may lead to effective treatments.

Paradoxically, an opportunity that was unavailable with SARS, MERS or Ebola has arisen because of the intense, globally distributed focus of medical and scientific professionals on COVID-19 that is providing a wealth of highly diverse information and data types. Nine bronchoalveolar lavage (BAL) samples were originally collected from patients in Wuhan China for RNA sequencing in order to determine the etiological agent for COVID-19 and resulted in the sequence of the first SARS-CoV-2 viral genome. However, the human reads from these samples were discarded 3. Here, we analyze the human RNA-seq data from these BAL samples alongside 40 controls.

Results and Discussion

The Renin Angiotensin System (RAS)

Although pre-existing hypertension is a reported comorbidity for COVID-19, recent reports indicate hypotension is highly associated with COVID-19 patients once in the hospital (Rentsch, 2020). The RAS is an important pathway linked to these conditions because it maintains a balance of fluid volume and pressure using several cleavage products of the peptide angiotensin (AGT) and their receptors (Arendse et al., 2019, Flores-Muñoz et al., 2011, Carey, 2017). The most well-studied peptide is angiotensin II (Ang II), which typically generates vasoconstriction and sodium retention via the AGTR1 receptor and vasodilation and natriuresis when binding to the AGTR2 receptor. The RAS also includes several other lesser known peptides that are highly important; Ang1-7 binds to the MAS1 receptor, generating anti-inflammatory and vasodilatory effects, and Ang1-9 binds to the AGTR2 receptor. Ang II is produced by the enzyme ACE whereas Ang1-7 is generated by the combination of ACE and ACE2 activity and Ang1-9 by ACE2 alone. It is important, therefore, to consider all of these components in the context of the others and not any one in isolation.

ACE2 is also the main receptor for the SARS-CoV-2 virus and is not highly expressed in normal lung tissue based on the Genotype-Tissue Expression (GTEx, gtexportal.org) six population.

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However, results from our differential gene expression analysis of RAS genes in cells taken from BAL samples from individuals presenting with severe symptoms of COVID-19 (Zhou et al., 2020) demonstrates upregulation of ACE2 (199 fold) and disruption of this system compared to controls. In the COVID-19 samples, AGT (34 fold) and the enzyme that activates it (REN, 380 fold) are increased compared to controls whereas the enzymes that produce most of the cleavage products, including ACE (−8 fold), are downregulated, which will likely result in a shift of the entire RAS to produce Ang1-9. In addition, the AGTR1 (430 fold) and AGTR2 (177 fold) receptors are upregulated in BAL COVID-19 samples.

Given the central role that the angiotensin and bradykinin (BK) peptides play in COVID-19 based on our gene expression analysis from BAL samples, we next focused on the RAS- and BK-related gene pathways in lung tissue from the GTEx population; specifically, the networks of genes that are correlated and ani-correlated with the expression of the angiotensin receptors AGTR2 and AGTR1. This subset of genes was annotated with functional information and cell type involvement which resulted in a network (Figure 1) that, as would be expected, demonstrates their extensive involvement in arterial and vascular resistance and blood flow via microvascular dilation, flow, and fluid balance. The genes on the left side of the network are extensively involved in vasoconstriction and contain, among others, ACE, AGTR1, BDKR2, Nitric Oxide Synthase-1, and −2 (NOS1 and NOS2). The right side of the network is extensively involved in decreased arteriolar resistance (vasodilation), increased vascular permeabilization, and altered fluid balance and includes, among other genes, ACE2, AGTR2, and the Vitamin D Receptor (VDR). Surprisingly, we find that both sides of the network are also clearly involved in immune system modulation.

Figure 1

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Functionally annotated network of genes involved in the hypertension-hypotension axis whose expression across the GTEx population is correlated and anticorrelated with the AGTR1 and AGTR2 receptors.
When ACE is downregulated and ACE2 and the BK pathway is upregulated in the lungs of COVID-19 patients it leads to the hypotension, vascular permeability, and the Bradykinin Storm that explains much … see more

The bradykinin system

Although not as widely discussed as angiotensin, BK is another potent regulator of blood pressure and can be considered essentially an extension of the RAS (Schmaier, 2002). Briefly, similar to the angiotensin peptides, BK is produced from an inactive pre-protein kininogen (either circulating - HMWK or tissue - LWMK) through activation by the serine protease kallikrein (Figure 2A). Kallikrein is represented by a cluster of serine proteases (KLK1-KLK15) on chromosome 19 with different tissue distributions; KLKB1 (on chromosome 4) is normally expressed in the pancreas and is responsible for circulating (plasma) kallikrein. These proteases are inactivated by zinc and several are known co-receptors for viruses including influenza (Kalinska et al., 2016). KLKB1 is activated by FXII of the intrinsic coagulation pathway, which is normally kept in check by the C1-Inhibitor encoded by SERPING1 (Figure 2A). This has the vital ancillary effect of inhibiting the feedback loop of FXII activation by kallikrein (Kaplan and Ghebrehiwet, 2010).

Figure 2

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Critically disrupted RAS and Bradykinin pathways in COVID-19 BAL samples.
(**A**) Significantly differentially expressed genes: red ovals indicate genes upregulated in COVID-19, blue are downregulated, colors are scaled to the log2-fold-change values for COVID-19. The overall … see more

Similar to AGTR2 stimulation, BK induces vasodilation, natriuresis, and hypotension upon activation of the BDKRB2 receptor. BK is tightly integrated with the RAS as BK receptor signaling is augmented by Ang1-9 , likely by resensitization of the BDKRB2 receptor (Chen et al., 2005; Marcic et al., 1999; Erdös et al., 2002) and also because ACE degrades and inactivates BK. Interestingly, ACE has a higher affinity for BK than it does for AGT (Cyr et al., 2001) and therefore under conditions where ACE is low, the vasopressor system is tilted toward a BK-directed hypotensive axis (Figure 2A). In addition to its role in pressure and fluid homeostasis, BK is a normal part of the inflammatory response after injury and acts to induce pain via stimulation of the BDKRB1 receptor by BK1-8 (Jacox et al., 2014), which also causes neutrophil recruitment and increases in **vascular permeability** (Stuardo et al., 2004; Araújo et al., 2001; Hofman et al., 2016; Figure 2B). BK1-8 is produced by the enzyme carboxypeptidase N (CPN1 671 fold) acting on BK.

As with the RAS, the BK system is also severely affected in the COVID-19 BAL samples. The expression of the BK precursor kininogen and nearly all of the kallikreins are undetected in controls but expressed in COVID-19 BAL (Figure 2A). Most of the enzymes that degrade BK, including ACE, are downregulated (−8 fold) in COVID-19 BAL compared to controls, directing BK1-9 and BK1-8 to the upregulated receptors BKB2R (207 fold) and BKB1R (2945 fold), respectively. Of note, the pain-receptor BKB1R is normally tightly controlled and expressed only at very low levels in nearly all tissues in GTEx, but in the case of COVID-19 BAL, both BK receptors are expressed whereas they are virtually undetected in controls. Finally, F12 is unchanged but the SERPING1 (−33 fold) gene that encodes the C1-Inhibitor that inhibits FXII is highly down-regulated, which would result in even further increases in BK in COVID-19 patients given its role in KLKB1 activation (Schmaier, 2016). As described below, the resulting Bradykinin Storm is likely responsible for most of the observed COVID-19 symptoms.

Hyaluronic Acid synthesis and degradation

Hyaluronic acid (HA) is a polysaccharide found in most connective tissues. HA can trap roughly 1000 times its weight in water (Cowman and Matsuoka, 2005) and when bound to water the resulting hydrogel obtains a stiff viscous quality similar to ‘Jello’ (Necas et al., 2008). HAS1, HAS2 and HAS3 are genes that encode hyaluronan synthases which are integral membrane proteins responsible for HA production (Necas et al., 2008). HA is degraded by hyaluronidases encoded by HYAL1 and HYAL2. Proteins encoded by other genes in this family (HYAL3 and HYAL4) do not appear to have a hyaluronidase activity (Harada and Takahashi, 2007; Kaneiwa et al., 2010). HYAL1 encodes a lysosomal hyaluronidase (Hyal-1) active at low pH and is responsible for intracellular degradation of HA (Harada and Takahashi, 2007). HYAL2 encodes a membrane-bound hyaluronidase (Hyal-2) responsible for extracellular degradation of HA (Harada and Takahashi, 2007). Both Hyal-1 and Hyal-2 are dependent on CD44 (an HA receptor) for activity (Harada and Takahashi, 2007).

As with the RAS and BK systems, the genes encoding HA synthesis and degradation are also severely affected in the COVID-19 BAL samples. There is significant upregulation of the genes involved in HA synthesis: HAS1 (9113 fold), HAS2 (493 fold), and HAS3 (32 fold). The CD44 gene that encodes the HA receptor required for HA degradation and the gene encoding extracellular hyaluronidase HYAL2 are both downregulated (−11 and −5 fold respectively) in the

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BAL fluid of COVID-19 patients. HYAL1 is not expressed in the BAL fluid of controls or the COVID-19 patients. The result of these shifts in expression would be likely to cause an increase in the amount of HA in the bronchoalveolar space of the lungs which, combined with the vascular hyperpermeability caused by BK, could form a viscous hydrogel that would negatively impact gas exchange (Figure 3). In fact, HA in BAL fluid has previously been associated with acute respiratory distress syndrome (ARDS) where there was a significant anticorrelation between the concentration of HA and the pulmonary oxygenation index (Modig and Hällgren, 1989; Hällgren et al., 1989). HA has also been associated with pulmonary thrombosis and/or ground glass opacities in radiological findings (Bhagat et al., 2012; Han et al., 2019; Jang et al., 2014).

Figure 3

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The upregulation of hyaluronan synthases and downregulation of hyaluronidases combined with the BK-induced hyperpermeability of the lung microvasculature leads to the formation of a HA-hydrogel that inhibits gas exchange in the alveoli of COVID-19 patients.

Although not the focus of the present study, coagulopathy is commonly reported in cases of COVID- 19 (The Lancet Haematology, 2020), and there are suggestions in the literature of links between RAS and coagulopathy. The Ang1-9 peptide that is increased in COVID-19 BAL stimulates thrombosis by inhibiting fibrinolysis (Mogielnicki et al., 2014). In addition to BK, ACE also degrades the antifibrotic peptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), which is produced from thymosin beta-4 (TMSB4X, −130 fold) (Kanasaki, 2020). Increased fibrinolysis could therefore be achieved by increasing ACE, or by administering thymosin beta-4, which is currently in clinical trials for the treatment of cardiovascular disorders (Timbetasin). If TMSB4X is, in fact, protective, it could explain the lower incidence of COVID-19 induced mortality in women (Jin et al., 2020) because it is found on the X chromosome and escapes X-inactivation. Women therefore would have twice the levels of this protein than men, which is supported by our BAL analysis (−207 fold in males, −131 fold in females).

In addition, both the RAS and BK pathways have previously been tied to HA . It was found that Angiotensin II increased CD44 expression and hyaluronidase activity (Bai et al., 2016). As discussed above, COVID-19 likely significantly downregulates the production of Angiotensin II which is consistent with the decrease in CD44 expression that is seen in the BAL fluid of SARS-CoV-2 infected patients. Furthermore, IL2 was recently reported to be highly upregulated in symptomatic but not asymptomatic COVID-19 patients (Long et al., 2020; Paegelow et al., 1995; Mustafa et al., 2002) and is upregulated (21 fold) in the BAL samples compared to controls. This cytokine is induced by BK in the lung, and causes vascular leakage syndrome (VLS), which appears to be mediated through CD44. Interestingly, CD44 knockout mice displayed reduced IL2-induced VLS, suggesting this may be a valuable target for COVID-19 intervention.

Clinical description of COVID-19

According to the CDC, the majority of SARS-CoV-2 infections are asymptomatic or mild. Those that proceed to more severe forms present with fever, a non-productive cough that may result in hemoptysis and shortness of breath. Other common symptoms are myalgia, fatigue, sore throat, nausea, vomiting, diarrhea, conjunctivitis, anorexia, and headache (cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html). Reports from blood studies include leukopenia, eosinopenia, neutrophilia, elevated liver enzymes, C-reactive protein, and ferritin (Fan et al., 2020; Huang et al., 2020; Goyal et al., 2020). Furthermore, autopsies have reported extensive hyaline membrane formation in the lungs of COVID-19 patients (Barton et al., 2020; Xu

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et al., 2020; Adachi et al., 2020; Mong et al., 2020). Specifically, histological analysis of the lungs of a deceased COVID-19 patient showed organizing hyaline membranes in the early stages of alveolar lesions and prominent hyaline membranes in the exudative phase of diffuse alveolar damage (Adachi et al., 2020). In a seperate post mortem study of lung tissue from COVID-19 patients, microscopic examination found 'numerous hyaline membranes without evidence of interstitial organization' (Barton et al., 2020). Furthermore, in another autopsy study of a COVID-19 patient, histological analysis found extensive hyaline membranes, which the authors interpreted as indicative of ARDS (Xu et al., 2020). Finally, a meta-analysis showed that there was a statistically significant 4.6 fold difference in lung weight of COVID-19 patients versus controls, which they conclude is consistent with the HA-hydrogel formation known to occur in ARDS (Mong et al., 2020).

Although much focus has been on the lung due to the need for ventilator support of end-stage disease, COVID-19 also affects the intestine, liver, kidney, heart, brain, and eyes (Wadman, 2020). Nearly one-fifth of hospitalized patients experience cardiac injury (Shi et al., 2020), many of whom have had no history of cardiovascular problems prior to infection. Responses include acute myocardial injury, myocarditis, and arrhythmias (Driggin et al., 2020) that may be due to viral infection directly, which is consistent with high expression of the SARS-CoV-2 receptor ACE2 in cardiac tissue (gtexporta.org). An important extension of the RAS in controlling cardiac contraction and blood pressure is the potent inotrope apelin (APLN), which acts as an NO-dependent vasodilator when its receptor (APLNR) heterodimerizes with BDKRB1 (Bai et al., 2014). APLN (98 fold), APLNR (3190 fold) and BDKRB1 (2945 fold) are all upregulated in COVID-19 BAL. As with BK and ANG derived peptides, APLN is inactivated by Neprilysin (MME), which is significantly downregulated in the BAL samples from COVID-19 individuals (−16 fold). Therefore, increased APLN-signaling can be added to the imbalanced RAS.

In addition to cardiac dysfunction, neurological involvement in COVID-19 was revealed after an MRI assessment of COVID-19-positive patients with encephalopathy symptoms in France identified enhancement in leptomeningeal spaces and bilateral frontotemporal hypoperfusion (Helms et al., 2020) which are consistent with increased vascular permeabilization in the brain. Furthermore, earlier reports from China indicate high frequencies of dizziness, headache, as well as taste and smell impairment (Mao et al., 2020). The most recent reports from the United States and China indicate that 30–50% of COVID-19 patients experience adverse gastrointestinal symptoms (Cholankeril, 2020; Pan et al., 2020). Direct infection by the virus and damage to the kidney was also observed, specifically in the proximal tubules (Su et al., 2020). These latter two findings are not surprising given the higher expression of ACE2 in these tissues compared to tissues overall (gtexportal.org), which would facilitate infection by the virus. Finally, COVID-19 patients also frequently display skin rashes including 'covid-toe' that appear to be related to dysfunction of the underlying vasculature.

Bradykinin Storms: A model of SARS-CoV-2, COVID-19, and BK-driven Vascular Permeabilization

Based on previous work in SARS-CoV-1 and SARS-CoV-2, it is likely that this new coronavirus enters host cells in nasal passages where the receptor ACE2 is moderately expressed. Migration to throat tissues and passage through the stomach is then possible given that SARS-CoV-2 can survive the extreme pH of the gastric tissues (Chin et al., 2020) and infection could then expand into the intestines where ACE2 levels are high (GTEx Consortium, 2013). Initial infection might not occur in the lung epithelium given that ACE2 is undetectable or expressed at extremely low levels there (GTEx Consortium, 2013). Following infection, the single polypeptide that is translated from the virus' positive-strand RNA genome is cleaved into active proteins by the non-structural protein 3CLpro protease. This protein is then repurposed by the virus to inactivate the

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host cells' first line of defense, interferon, most likely by degrading the NFkappaB activating factor IKK-gamma as has been shown to happen in the porcine coronavirus PEDV (Wang et al., 2016).

Aside from self-protection, the suppression of NFkappaB (−9 fold reduced in BAL samples) directly affects the RAS as NFkappaB normally induces the expression of ACE by binding to its promoter and increasing transcription (Garcia et al., 2016; Figure 2A). This likely relates to the role of ACE in the innate immune response that is independent of its actions on the vascular system (Bernstein et al., 2018). The virus therefore acts pharmacologically as an ACE inhibitor by reducing its RNA expression more than 10-fold, which is supported by our BAL RNA-seq analysis. Additionally, ACE2 expression is normally downregulated in-part by Ang II (Patel et al., 2016). As Ang II is the catalytic product of ACE, it would seem that the virus's ability to decrease ACE expression would have the effect of upregulating ACE2 (199 fold in our BAL analysis). In some patients, severe pulmonary involvement could occur when the virus is introduced into the intestinal lymph vessels and moves up the lymphatic system (Chen, 2020), enters the bloodstream at the thoracic duct and moves through the heart and into the lung microvasculature where it could attack cells in the lungs that now express ACE2 due to virus-induced upregulation.

Given that the high levels of ACE in the vascular bed of the lung are the major producer for circulating angiotensin-derived peptides (Studdy et al., 1983), establishment of SARS-CoV-2 in the lung will have profound effects. Downregulation of ACE here (confirmed in BAL samples from COVID-19 patients) will result in the diversion of the RAS to produce the BK-augmenting peptide Ang1-9, exacerbating BK-effects, such as pain sensitization and increased vascular permeability on a system-wide level. Expansion of this imbalance as described above (Figure 2), increases levels of BK and will result in increased vascular permeability in tissues that have been infected by SARS-CoV-2 and be most severe in those that are normally regulated by ACE. ACE may also provide a key diagnostic point as half of the variation amongst individuals can be explained by an insertion/deletion polymorphism of the gene (Rigat et al., 1990).

As mentioned above, the combination of vascular permeability and HA build up in the lungs could produce a hydrogel that significantly inhibits gas exchange in bronchoalveolar spaces. This is consistent with the autopsy reports of hyaline membranes in the lungs of deceased COVID-19 patients as well as other acute respiratory distress conditions (e.g., SARS, MERS, ARDS) (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020) Although this likely represents a late-stage event in severe cases of COVID-19, if the cause is overproduction of HA as a result of disruption of the RAS, it is also a potentially valuable intervention point because the condition is easily identified, and treatment could have rapid and significant beneficial effects.

In addition, increased levels of the vasodilating peptide APLN that are produced in COVID-19 patients could have spillover effects on cardiac function. APLN upregulates the expression of ACE2 (Sato et al., 2013) and directly affects cardiac contraction and vasodilation. Increased levels of APLN are known to be associated with cardiac arrhythmia (Salska et al., 2018) and in the case of hyper-stimulated BK output, could be causing cardiac events in COVID-19 patients. In addition, increased levels of APLN could lead to more ACE2 receptors for SARS-CoV-2 in the heart and thus stimulate further infection.

Furthermore, excess BK can lead to hypokalemia (Zhang et al., 2018), which is associated with arrhythmia and sudden cardiac death (Kjeldsen, 2010), (Bielecka-Dabrowa et al., 2012; Skogestad and Aronsen, 2018) , both of which have been reported in COVID-19 patients (Huang et al., 2020; Guo et al., 2020), (Wang et al., 2020) ; a recent report confirms that hypokalemia is

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occurring in severe cases of COVID-19 (Lippi et al., 2020). It is also notable that many of the other symptoms being reported for COVID-19 (myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, decreased cognitive function) are remarkably similar to other hyper-BK-conditions that lead to vascular hyper-permeabilization such as angioedema as was recently noted (van de Veerdonk et al., 2020). In agreement with that report, our results indicate that the pathology of COVID-19 is likely the result of Bradykinin Storms rather than cytokine storms (although given the induction of IL2 by BK, the two may be intricately linked). This model predicted that a loss of ACE2 would exacerbate the BK-induced pathogenesis (van de Veerdonk et al., 2020). However, the BAL fluid expression data indicate that the Bradykinin Storm is instead caused by upregulation of ACE2 and reduced degradation of BK by ACE. Based on this data-driven model, an individual's symptomatology is likely directly related to the specific tissue distribution of viral infection around the body (Figure 4) and should be viewed in the context of an overactive bradykinin response. The majority of circulating BK is degraded in the lungs by ACE and therefore heterogeneous symptoms of COVID-19 could also be the result of systemic effects of increased levels of circulating bradykinin and the eight-fold reduction of ACE in the lung microvasculature that would normally degrade it.

Figure 4

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Systemic-level effects of critically imbalanced RAS and BK pathways.
The gene expression patterns from COVID BAL samples reveal a RAS that is skewed toward low levels of ACE that result in higher levels of Ang1-9 and BK. High levels of ACE normally present in the … see more

Given this model, factors that affect RAS balance should be further investigated in the framework of diagnosis and treatment. For example, another well-documented regulator of RAS is Vitamin D (Vaidya and Williams, 2012) as the liganded Vitamin D receptor (VDR) suppresses REN expression. Patients who are deficient in Vitamin D are at-risk for ARDS in general (Dancer et al., 2015) and Vitamin D deficiencies have recently been associated with severity of illness in COVID-19 patients (Alipio, 2020). Our BAL gene expression analysis shows that VDR is 2-fold down-regulated and enzymes [CYP24A1 (465 fold), CYP3A4 (208 fold)] that catabolize Vitamin D (1,25(OH)2D) and its precursor (25OHD) (Bikle, 2014) are up-regulated in COVID-19 patients compared to controls, which will likely result in further increases in REN. Furthermore, our analysis of ChipSeq experiments from a VDR study Tuoresmäki et al., 2014 have determined that, in addition to REN, the following genes in the RAS-Bradykinin system have a VDR binding site within 20 kilobases: BDKRB1, BDKRB2, CYP24A1, DPP4, IKBKG (regulates NFkappaB), KLK1, KLK2, KLK4, KLK6, KLK7, KLK9, KLK10, and MME. Six of these binding sites can be tied to the following genes via chromatin structure with the use of H-MAGMA and Hi-C data (see Materials and methods): DPP4, BDKRB2, KLK6, KLK7, KLK10, and IKBKG. VDR binds to many sites in the genome with tissue-specific binding patterns so these putative associations to other genes in the RAS and BK pathways will require further investigation.

Potential interventions
Several interventional points (most of them already FDA-approved pharmaceuticals) could be explored with the goal of increasing ACE, decreasing BK, or blocking BK2 receptors (Table 1). Icatibant is a BKB2R antagonist (Dubois and Cohen, 2010) whereas Ecallantide acts to inhibit KLKB1, reducing levels of BK production (Farkas and Varga, 2011). Androgens (danazol and stanasolol) increase SERPING1, although the side effects likely make these undesirable (Wilkerson, 2012), but recombinant forms of SERPING1 (Berinert/Cinryze/Haegarda) could be administered to reduce BK levels. It should be noted that any intervention may need to be timed

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correctly given that REN levels rise on a diurnal cycle (Gordon et al., 1966), peaking at 4AM which corresponds with the commonly reported worsening of COVID-19 symptoms at night. Another approach would be the modulation of REN levels via Vitamin D supplementation when warranted. 4-methylumbelliferone (Hymecromone) is a potent inhibitor of HAS1, HAS2, and HAS3 gene expression and results in the suppression of the production of hyaluronan in an ARDS model (McKallip et al., 2003; McKallip et al., 2013). Hymecromone (4-methylumbelliferone) is approved for use in Asia and Europe for the treatment of biliary spasm. However, it can cause diarrhea with subsequent hypokalemia, so considerable caution should be used if this were to be tried with COVID-19 patients (NCATS Inxight, 2020). As mentioned above, Timbetasin may reduce COVID-19 related coagulopathies by increasing fibrinolysis.

Table 1

Potential therapeutic interventions, their targets, and predicted effect.

Drug	Target	Predicted Effect
Danazol, Stanozolol	SERPING1	Reduce Bradykinin production
Icatibant	BKB2R	Reduce Bradykinin signaling
Ecallantide	KLKB1	Reduce Bradykinin production
Berinert,Cinryze,Haegarda	SERPING1	Reduce Bradykinin production
Vitamin D	REN	Reduce Renin production
Hymecromone	HAS1,HAS2, HAS3	Reduce hyaluronan
Timbetasin	TMSB4X	Increase fibrinolysis

The testing of any of these pharmaceutical interventions should be done in well-designed clinical trials. Given the likely future outbreaks of zoonotic viruses with a similar outcome, it would be in the best interest long-term to invest in the development of small molecules that can inhibit the virus from replicating or suppressing the host immune system such as a 3CLpro inhibitor. However, to date, no large multi-centered, randomized, placebo controlled, blinded clinical trials have been done with 3CLpro inhibitors (Sisay, 2020). In the meantime, our analyses suggest that prevention and treatment centered on vascular hyper-permeability and the suppression of hyaluronan may prove beneficial in fighting the pathogenesis of COVID-19. Given the fact that two recent studies have validated our model's predictions of hypokalemia (Lippi et al., 2020) and Vitamin D deficiency (Alipio, 2020) in COVID-19 patients, we suggest that rapid testing of the pharmaceutical interventions discussed above is warranted.

Decision letter

- **Frank L van de Veerdonk** Reviewing Editor; Radboud University Medical Center, Netherlands
- **Jos WM van der Meer** Senior Editor; Radboud University Medical Centre, Netherlands
- **Frank L van de Veerdonk**Reviewer; Radboud University Medical Center, Netherlands
- **Roger Little** Reviewer

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In the interests of transparency, eLife publishes the most substantive revision requests and the accompanying author responses.

Acceptance summary:

The manuscript has highlighted a core response in COVID-19 with RAS and bradykinin which is really a different signature than any other viral pneumonia other than coronavirus infection. This supports the importance of these pathways in coronavirus and contributes to a better understanding of COVID-19. The novelty and importance is also the site of infection (the lungs) that has been studied for this signature which really adds novelty to the existing literature.

Decision letter after peer review:

Thank you for submitting your article "A Mechanistic Model and Therapeutic Interventions for COVID-19 Involving a RAS-Mediated Bradykinin Storm" for consideration by *eLife*. Your article has been reviewed by three peer reviewers, including Frank L van de Veerdonk as the Reviewing Editor and Reviewer #1, and the evaluation has been overseen by Jos van der Meer as the Senior Editor. The following individual involved in review of your submission has agreed to reveal their identity: Roger Little (Reviewer #3).

The reviewers have discussed the reviews with one another and the Reviewing Editor has drafted this decision to help you prepare a revised submission.

We would like to draw your attention to changes in our revision policy that we have made in response to COVID-19 (https://elifesciences.org/articles/57162). Specifically, we are asking editors to accept without delay manuscripts, like yours, that they judge can stand as *eLife* papers without additional data, even if they feel that they would make the manuscript stronger. Thus the revisions requested below only address clarity and presentation.

Summary:

The authors have used a systems biology approach and analyzed data from BAL (9 COVID patients) with 40 control BALs. They clearly demonstrate a signature of a dysregulated RAAS and KKS. Further analysis shows the signature is skewed towards an incapacity to dampen the KKS and bradykinin production that might lead to a bradykinin storm that could contribute to the endothelial dysfunction that results in vascular leakage seen in the early stages of patients admitted to the hospital with COVID. The data are timely, conclusions supported by the data and the BAL sample analysis provides real novel data.

Figure 2: Please designate Figure 2 into two panels: A and B, since it is later refered to in this way in the text. It would also be helpful to illustrate the scale so one can observe the large disruption of the system. The scale only goes to 5 in both directions, and being able to see the extreme over-expression would improve the argument that components of the BK system are overexpressed.

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Subsection “Hyaluronic Acid Synthesis and Degradation”. It would be helpful to add a sentence of two to expand on the pulmonary thrombosis evidence, as it's known that thrombosis is observed in some Covid-19 patients. It could possibly be added in the third paragraph below.

Subsection “Bradykinin Storms: A Model of SARS-CoV-2, COVID-19, and BK-driven Vascular Permeabilization” third paragraph. The HA hypothesis is compelling and potentially explanatory for the hypoxia observed in Covid-19 patients. This hypothesis would be better supported by a representation of the data referenced here (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020), as opposed to just stating that HA buildup is observed. Either a discussion or even a table would be useful with referenced data.

Same section paragraph five. Here again, it would be useful to represent the studies mentioned here (van de Veerdonk et al., 2020) with similar phenotypic observations to Covid-19. Additional discussion of the data from that paper, or even better the addition of a table with referenced data is suggested. The BK hypothesis is a strong and central hypothesis of this paper and it would be better supported with more than just a statement and a reference.

The results of the ChipSeq analysis should be further described. Most importantly, what is the significance of the binding site within 20 kilobases? It seems like a lot of genomic real estate to make an assertion that there is some effect. Is there any evidence this proximity results in activation or deactivation? If so please provide a reference.

Subsection “Potential Interventions”: Another suggestion here to include a table with suggested interventions -> targets -> drugs -> expected effects.

Supplementary figures S1 and S2 could be represented by single tables and also made available in.xls forms.

508) 2020-07-07 Casadevall A, Joyner MJ, Pirofski LA: SARS-CoV-2 viral load and antibody responses: the case for convalescent plasma therapy. J Clinical Investigation 2020 Jul 7; 130 (10): 5112-5114. https://www.jci.org/articles/view/139760/pdf

509) 2020-07-07 U.S. Department of Health and Human Services: HSS, DOD collaborate with Regeneron on large scale manufacturing demonstration project of COVID-19 investigational therapeutic treatment. ASPR Press Office, 202-205-8117. https://www.hhs.gov/about/news/2020/07/07/hhs-dod-collaborate-regeneron-large-scale-manufacturing-demonstration-project-covid-19-investigational-therapeutic-treatment.html

510) 2020-07-07 Blankenship K: Regeneron bags $450M deal with U.S. Government for coronavirus antibody cocktail supply. Fierce Pharma. https://www.fiercepharma.com/manufacturing/regeneron-bags-450m-deal-u-s-government-for-covid-19-antibody-cocktail

511) 2020-07-07 Regeneron: Regeneron announces manufacturing and supply agreement for Barda and U.S. Department of Defense for REGN-COV2 anti-viral antibody cocktail. Investor Regeneron https://investor.regeneron.com/node/24026/pdf

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512) 2020-07-07 Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D: A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. eLife 2020 Jul 7; 9: e59177. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7410499/

513) 2020-07-09 Thomas K: These scientists raced to find a Covid-19 drug. Then the virus found them. The New York Times https://www.nytimes.com/2020/07/09/health/regeneron-monoclonal-antibodies.html

514) 2020-07-09 Guarascio F: EU raises its bet on blood plasma in search for COVID-19 therapy. Reuters. https://www.reuters.com/article/us-health-coronavirus-eu-plasma/eu-raises-its-bet-on-blood-plasma-in-search-for-covid-19-therapy-idUSKBN24A1N2

515) 2020-07-10 Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC: Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease (COVID-19) A Review. JAMA.2020;324(8):782-793.doi:10.1001/jama.2020.12839 https://jamanetwork.com/journals/jama/fullarticle/2768391

516) 2020-07-10 Gillenwater S, Rahaghi F, Hadeh A; McMahon JH, Udy A, Peleg AY; McCaw ZR, Kim DH, Wei LJ; Olalla J; Beigel JH, Tomashek KM, Dodd LE: Letters to the Editor regarding "Remdesivir for the treatment of Covid-19 – Preliminary report." Published July 10, 2020, at NEJM.org and subsequently published N Engl J Med September 3, 2020; 383: 992-994. https://www.nejm.org/doi/pdf/10.1056/NEJMc2022236?listPDF=true

517) 2020-07-10 World Health Organization: Guidance on maintaining a safe and adequate blood supply during the coronavirus disease 2019 (COVID-19) pandemic and on the collection of COVID-19 convalescent plasma: interim guidance, 10 July 2020. https://apps.who.int/iris/handle/10665/333182 and https://apps.who.int/iris/bitstream/handle/10665/333182/WHO-2019-nCoV-BloodSupply-2020.2-eng.pdf?sequence=1&isAllowed=y

518) 2020-07-13 Sharun K, Tiwari R, Yatoo MI, Patel SK, Natesan S, Dhama J, Malik YSS, Harapan H, Singh RK, Dhama K: Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects, Expert Opinion on Biological Therapy, 20:9, 1033-1046, DOI: 10.1080/14712598.2020.1796963 https://www.tandfonline.com/doi/pdf/10.1080/14712598.2020.1796963?needAccess=true

519) 2020-07-16 Zhou L, Wang J, Liu G, Lu G, Lu Q, Dong R, Tian G, Yang J, Peng L: Probing antiviral drugs against SARS-CoV-2 through virus-drug association prediction based on the KATZ method. Genomics 2020; 112: 4427-4434. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7832256/pdf/main.pdf

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520) 2020-07-17 Wortham JM, Lee JT, Althomsons S, Latash J, Davidson A, Guerra K, Murray K, *et.al.*: Characteristics of persons who died with COVID-19.—United States, February 12 – May 18, 2020. Morbidity and Mortality Weekly Report (MMWR), July 17, 2020; 69 (28): 923-929. https://www.cdc.gov/mmwr/volumes/69/wr/mm6928e1.htm

521) 2020-07-19 Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, Wiggins CC, Senefeld JW, Klompas AM, Hodge DO, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimabal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Soto JCD, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS. COVID-19 Convalescent Plasma in 20,000 hospitalized patients. Mayo Clin Proc September 2020; 95(9): 1888-1897. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7368917/pdf/main.pdf

522) 2020-07-22 Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049. https://web.archive.org/web/20210904020833/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=6&ti=1%2C6&Search_Arg=andrus+charles+h&Search_Code=NALL&CNT=25&PID=cXfFuGrmHQvLVlLvfNNt7Yjwh73ImgQ&SEQ=20210512081428&SID=1

523) 2020-07-28 World Health Organization: WHO Webinar on collection of COVID-19 convalescent plasma. https://www.who.int/news-room/events/detail/2020/07/28/default-calendar/who-webinar-on-collection-of-covid-19-convalescent-plasma

524) 2020-07-28 White DB, Angus DC: A proposed lottery system to allocate scarce COVID-19 medications. Promoting fairness and generating knowledge. JAMA 2020 Jul 28; 324 (4): 329-330. https://jamanetwork.com/journals/jama/fullarticle/2767751

525) 2020-07-29 Cevik M. Tate M, Lloyd O, Maraolo A, Schafers J, Ho A: SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. (Preprint 7-29-2020) Epub 2020 Nov 19; Lancet Microbe 2021 Jan;2(1):e13-e22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7837230/pdf/main.pdf

526) 2020-07-30 Adamy J: Families file first wave of Covid-19 lawsuits against companies over worker deaths—Coronavirus victims and their families allege workplaces failed to protect them. Wall Street Journal 30 Jul 2020. https://www.wsj.com/articles/families-file-first-wave-of-covid-19-lawsuits-against-companies-over-worker-deaths-11596137454

527) 2020-07-30 American Red Cross: President Trump visits the American Red Cross. To highlight need for convalescent plasma during COVID-19. https://www.redcross.org/about-

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us/news-and-events/press-release/2020/red-cross-highlights-need-for-convalescent-plasma-during-covid-19.html

528) 2020-07-30 Hahn S: Plasma Donation – PSA. (*Appeal by the FDA Commissioner on the same day as the American Red Cross visit by President Trump soliciting patients recovering from COVID-19 to donate COVID-19 Convalescent Plasma.)* https://www.youtube.com/watch?v=PlX15rWdBbY

529) 2020-07-30 Howard Bauchner, M.D., JAMA Editor-in-Chief, Interview of FDA Commissioner, Stephen Hahn, M.D. https://www.youtube.com/watch?v=UdmaU2-C_wE

530) 2020-07-30 McKend E: Dr. Birx: Plasma donations needed as coronavirus cases spike nationwide. https://spectrumnews1.com/ky/lexington/health/2020/07/30/dr--birx--plasma-donations-needed-as-coronavirus-cases-spike-nationwide

531) 2020-07-31 FDA: Donate COVID-19 plasma. http://web.archive.org/web/20200731065328/https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma First attachment of "Dr. Hahn – Plasma Donation – PSA", https://www.youtube.com/watch?v=PlX15rWdBbY [Initially posting April 14, 2020].

532) 2020-08-03 AEI: Op-ed, 4 former FDA commissioners: Blood plasma might be the COVID-19 treatment we need. The Washington Post https://www.aei.org/op-eds/4-former-fda-commissioners-blood-plasma-might-be-the-covid-19-treatment-we-need/

533) 2020-08-03 Alltucker K: 'We're in for a bad and rocky ride:' Ex-WHO doctor who helped eradicate smallpox predicts COVID-19 turmoil for years. USA TODAY, Published 8:15 p.m. ET Aug. 3, 2020 | Updated 1:41 p.m. ET Aug. 4, 2020. https://www.healthleadersmedia.com/covid-19/were-bad-and-rocky-ride-ex-who-doctor-who-helped-eradicate-smallpox-predicts-covid-19

> The world will be fighting coronavirus for the next three to four years as virus hot spots skip from nation to nation, and the pandemic's toll will linger for decades, said Dr. Larry Brilliant, a California epidemiologist who was part of a World Health Organization team in the 1970s that helped eradicate smallpox.
>
> But it's "not all doom and gloom," **with effective vaccines likely to emerge from dozens of candidates worldwide and effective treatments, including convalescent plasma and monoclonal antibodies, to help people recover more quickly**, said Brilliant, who chairs Ending Pandemics advisory board.
>
> "We will still be chasing the virus four years from now. But it won't be like (today)," Brilliant told the USA TODAY Editorial Board on Monday afternoon. "It will be like the smallpox eradication program. The polio eradication program. Having yellow fever in some countries and not in others."

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534) 2020-08-03 Sharun K, Tiwari R, Iqbal Yatoo M: Patel SK, Natesan S, Dhama J: Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects. Expert Opinion on Biological Therapy. 2020; 20 (9): 1033-1046. https://www.tandfonline.com/doi/pdf/10.1080/14712598.2020.1796963?needAccess=true

535) 2020-08-04 Thomas K, Weiland N: As Trump praises plasma, researchers struggle to finish critical studies. New York Times https://www.nytimes.com/2020/08/04/health/trump-plasma.html

536) 2020-08-04 Dockser Marcus A: Convalescent plasma reduced death rate among Covid-19 patients, study data signals—Hospitalized patients who got earlier transfusions of blood plasma rich in antibodies to the coronavirus show a lower mortality rate. Wall Street Journal. https://www.wsj.com/articles/convalescent-plasma-reduced-death-rate-among-covid-19-patients-study-data-signals-11596594390

> Hospitalized Covid-19 patients who received transfusions of blood plasma rich with antibodies from recovered patients reduced their mortality rate by about 50%, according to researchers running a large national study.
>
> The researchers presented their data analysis Saturday in a webinar for physicians interested in learning about so-called convalescent plasma, with data slides that were reviewed by The Wall Street Journal. The researchers said they saw signs that the treatment might be working in patients who received high levels of antibodies in plasma early in the course of their illness. They based their conclusions on an analysis of about 3,000 patients.
>
> Patients who at three days or less after diagnosis received plasma containing high levels of antibodies against the coronavirus had a mortality rate of 6.6% at seven days after the transfusion. That compared with a mortality rate of 13.3% for patients who got plasma with low levels of antibodies at four days or more after diagnosis. That indicates reduced mortality of about 50%, the researchers said.
>
> At 30 days after transfusion, the mortality rate was reduced by about 36%, investigators reported

537) 2020-08-04 Yong E: How the pandemic defeated America. The Atlantic. https://www.theatlantic.com/magazine/archive/2020/09/coronavirus-american-failure/614191/

538) 2020-08-06 Hegerova L, Gooley TA, Sweerus KA, Maree C, Bailey M, Dunleavy V, Patel K, Alcom K, Haley R, Johnsen JM, Konkle BA, Lahti AC, Alexander ML, Goldman JD, Lipke A, Lim S, Pauk JS, Pagel JM: Use of convalescent plasma in hospitalized patients with COVID-19: case series. Blood 6 August 2020; 136 (6): 759-762. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414587/pdf/main.pdf

> In conclusion, the current study suggests that CP use in **severe and critically ill patients with COVID-19 may improve survival if given early in the course of disease**. The efficacy as a

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potential therapy needs further study in well-designed trials to better understand the contribution of CP to outomes in COVID-19.

539) 2020-08-06 Bloch EM: Convalescent plasma to treat COVID-19. Convalescent plasma to treat COVID-19. Blood 6 August 2020; 136 (6): 654-655. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414591/pdf/main.pdf

In conclusion, observational studies and compassionate use programs have been instrumental in the mobilization of CCP to contend with a global health emergency. Although safety has been addressed, efficacy data are critically needed to transition CCP's status from an investigational product to a standard therapy. The latter has practical ramifications, offering a formal mechanism for reimbursement and thus durable treatment strategy. Broadly, COVID-19 presents a rare opportunity to study CP. If shown to be effective, CP would offer a scalable model that could be applied both to the current pandemic as well as to future emerging infectious diseases. It could also facilitate development of hyperimmune globulin and vaccine design. Clinical trials are already under way to address the uncertainty of use. Nonetheless, harmonization of efforts is needed along with creative approaches to overcome looming obstacles, such as pairing of trials of similar design and/or metanalysis. We must not be left wondering whether the intervention worked after the pandemic wanes.

540) 2020-08-06 Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, Li J, Wang Z, Wu W, Wu M, Li W, Li L, Cai Y, Bosco B, Zhong A, Liu X, Lv T, Gan Z, Chen G, Pan Y, Liu C, Zhang K, Xu X, Wang C, Wang Q: Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 6 August 2020; 136 (6): 755-758. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414593/pdf/main.pdf

Experience from SARS-CoV-1 shows that convalescent plasma is most effective when administered shortly after symptom onset, typically within 2 weeks.7,14,17 The study by Liu et al[16] showed that the effect of CCP was similar in an interval of 3 weeks' duration of symptoms. We compared the time to clinical improvement in patients with different therapy timings in our cohort, including 1 to 4 weeks, 5 to 6 weeks, 7 weeks, and 8 weeks after symptom onset. The results showed that the median time to clinical improvement was ;10 days in the 1 to 4 weeks', 5 to 6 weeks', and 7 weeks' groups. However, the time to clinical improvement was significantly prolonged in the $8 weeks' group (Figure 1I).

In summary, we analyzed a large cohort of patients with COVID19 who received CCP and provide detailed evidence regarding their clinical improvement. Although the homogeneous data obtained from a single center may reduce some biases, there could inevitably be some confounding factors (eg, biased patient assignments) in this retrospective study. In addition, complete data on neutralizing antibody titers in CCP units were not available, limiting the power of evaluating the correlation between the quality of donor plasma and efficacy. Moreover, a stratified analysis of cases of severe and critical patients could not be performed due to the low proportion of critical patients. This analysis differs from existing studies in that its dynamic laboratory observations using large-scale data make it possible to analyze the potential therapeutic mechanism of CCP, recognize the characteristics of responders and nonresponders, and identify the indications and timing of therapy.18 Our results suggest that CCP, transfused even after 2 weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in patients with severe or critical cases of COVID-19. We anticipate that this study could shed new light in clinical practice and monoclonal antibody development for COVID-19.

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541) 2020-08-06. Tobian AA, Shaz BH: Earlier the better: convalescent plasma. Blood 6 August 2020; 136 (6): 652-653. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414595/pdf/main.pdf

> Convalescent plasma is one of the best therapies currently available to treat COVID-19. However, critical questions on timing of treatment in the disease course and dose (volume and antibody titer levels) need to be answered. These answers will also help prepare us for other passive antibody treatments (eg, hyperimmune globulin made from convalescent plasma and monoclonal antibodies). The medical community must work together to battle this deadly disease in order to determine the best therapies and reduce mortality.

542) 2020-08-07 U.S. Food & Drug Administration: Donate COVID-19 Plasma. http://web.archive.org/web/20200816041956/https:/www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma

543) 2020-08-12 Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment. St. Louis Post-Dispatch Aug 12, 2020. https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_ccec0f56-4493-5a26-8601-45e35d364b2d.html

> Since April, the Trump administration has set aside **more than $300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.
>
> But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.
>
> "If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.
>
> Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

544) 2020-08-12 Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Soto JCD, Baker SE, Shepherd JRA, van Helmond N, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whenlan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL, Wright RS, Carter RE, Casadevall A: Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience. Version 1. medRxiv Preprint. 2020 Aug 12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430623/?report=printable

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Abstract …Participants: Adult participants enrolled and transfused under the purview of the US Convalescent Plasma EAP program between April4 and July 4, 2020 who were hospitalized with (or at risk of) severe or life threatening acute COVID-19 respiratory syndrome. Intervention: Transfusion of at least one unit of human COVID-19 convalescent plasma using standard transfusion guidelines at any time during hospitalization. Convalescent plasma was donated by recently-recovered COVID-19 survivors, and the antibody levels in the units collected were unknown at the time of transfusion. Main Outcomes and Measures: Seven and thirty-day mortality. Results: the 35,322 transfused patients had heterogeneous demographic and clinical characteristics. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis (p <0.0001).

545) 2020-08-17 U.S. Food & Drug Administration: Donate COVID-19 Plasma. http://web.archive.org/web/20200822062658/https:/www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma

546) 2020-08-19 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. August 19, 2020. https://web.archive.org/web/20200822210941/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

547) 2020-08-20 Xie J. Wu W, Li S, Hu Y, Hu M, Li J, Yang Y, Huang T, Zheng K, Wang Y, Kang H, Huang Y, Jiang L, Zhang W, Zhong M, Sang L, Zheng X, Pan C, Zheng R, Li X, Tong Z, Qui H, Du B: Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. Intensive Care Med 2020 Aug 20; 46: 1863-1872. https://link.springer.com/article/10.1007%2Fs00134-020-06211-2

548) 2020-08-11 Meini S, Zanichelli A, Sbromavacca R, Luri F, Roberts AT, Suffritti C, Tascini C: Understanding the pathophysiology of COVID-19: Could the contact system be the key? Frontiers in immunology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7432138/pdf/fimmu-11-02014.pdf

549) 2020-08-20 Pharmaceutical Technology: Roche teams up with Regeneron on Covid-19 therapy. https://www.pharmaceutical-technology.com/news/roche-regeneron-covid-therapy/

550) 2020-08-21 Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, Fulton BO, Yan Y, Koon K, Patel K, Chung KM, Hermann A, Ullman E, Cruz J, Rafique A, Huang T, Fairhurst J, Libertiny C, Malbec M, Lee W, Welsh R, Farr G, Pennington S, Deshpande D, Cheng J, Watty A, Bouffard P, Babb R, Levenkova N, Chen C, Zhang B, Romero Hernandez A, Saotome K,Zhou Y, Franklin M, Sivapalasingam S, Chien Kye D, Weston S, logue J, Haupt R, Frieman M, Chen G, Olson W, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA: Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody

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cocktail. Science 2020; 369 (6506): 1010-1014.
https://science.sciencemag.org/content/369/6506/1010

551) 2020-08-23 Trump D: Donald Trump August 23 White House COVID-19 Press Conference Transcript. Rev Aug 23, 2020. Video of the conference: https://www.youtube.com/watch?v=nE0EkrElCRk Transcript: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

Appendix 1 of a draft cover letter (never sent) to the President Biden of August 2021:

Transcript of August 23, 2021 White House press conference in its entirety: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

(The video of the August 23, 2020 White House press conference in its entirety: https://www.youtube.com/watch?v=nE0EkrElCRk)

President Donald Trump held an August 23 coronavirus press conference where he announced the FDA is issuing an emergency authorization for a COVID-19 treatment called convalescent plasma. Trump touted the approval as a "historic announcement." Read the full transcript of the press conference here.

Donald Trump: (01:38)
Thank you very much, and it's good to see you all. Hope you had a great weekend at your convention. We're going to have a great convention coming up, and I look forward to it.

Donald Trump: (01:51)
But before I discuss a very historic breakthrough in our fight against the China virus, I'd like to provide an update on the recent wildfires in California and the storms in the Gulf of Mexico. Yesterday, I approved a major disaster declaration for California, spoke to Governor Newsom as they battled two of the worst wildfires in the history of their state. That continues.

Donald Trump: (02:19)
The federal government has already deployed over 26,000 first responders and personnel to battle the wildfires. We're working very closely with the Governor and very closely with a lot of great state representatives and local representatives. We'll take care of the situation, but we have 26,000 first responders already. Our hearts go out to the thousands of families who have lost their homes, as we grieve for the families of two first responders and five residents who have tragically lost their lives in a very horrific fire, one of the biggest we've ever seen.

Donald Trump: (03:01)
My administration is also closely monitoring Hurricane Marco and Tropical Storm Laura, which are coming in rapidly. Hurricane Marco is expected to make landfall in Louisiana tomorrow, and Tropical Storm Laura is expected to hit Louisiana two days later. This is somewhat unprecedented, the scope of the storms, and also the fact that they come so quickly after one another. Both storms have the potential of gathering strength before they make landfall and could cause significant damage across the Gulf Coast and also in Puerto Rico. We have everybody stationed and ready to go in Puerto Rico and the Gulf Coast. We

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have tremendous, tremendous people. FEMA is lined up. We have the Coast Guard ready. The Coast Guard has done a fantastic job. They do such good work, and we want to thank our great Coast Guard.

Donald Trump: (03:58)
I'm asking all Americans in the storm's path to follow the instructions of your state and local governments very closely. I've approved emergency declarations for Puerto Rico and for Louisiana. FEMA is mobilized on the ground and is ready to help. They will be in there very quickly, very, very quickly. I spoke to Governor John Bel Edwards also of Louisiana, and I've informed him, and at his request also, a major disaster declaration is signed and ready to go. We have everybody ready in Puerto Rico, the Gulf Coast, Louisiana, and also on the forest fires in California. We have a great team. Unfortunately, we have some very, very powerful natural disasters.

Donald Trump: (04:47)
On the therapeutics front, this is what I've been looking to do for a long time. This is a great thing. Today, I'm pleased to make a truly historic announcement in our battle against the China virus that will save countless lives. The FDA has issued an Emergency Use Authorization, and a that's such a powerful term, Emergency Use Authorization, for a treatment known as convalescent plasma. This is a powerful therapy that transfuses very, very strong antibodies from the blood of recovered patients to help treat patients battling a current infection. It's had an incredible rate of success. Today's action will dramatically expand access to this treatment.

Donald Trump: (05:39)
I want to thank Dr. Hahn and Secretary Azar. I want to thank the FDA, all of the people that have been working very hard on this. It showed tremendous potential. It's only made possible because of Operation Warp Speed. That is everybody working together. We're years ahead of approvals that we would be if we went by the speed levels of past administration. We'd be two years, three years behind where we are today, and that includes on vaccines that you'll be hearing about very soon, very shortly.

Donald Trump: (06:16)
To deliver treatments and vaccine to save lives, we're removing unnecessary barriers and delays, not by cutting corners, but by marshaling the full power of the federal government. We provided $48 million to fund the Mayo Clinic study that tested the efficacy of convalescent plasma for patients with the virus. Through this study over 100,000 Americans have already enrolled to receive this treatment, and it is proven to reduce mortality by 35%. It's a tremendous number. The FDA, MIT, Harvard, and Mount Sinai Hospital have also found convalescent plasma to be a very effective method of fighting this horrible disease. Based on the science and the data, the FDA has made the independent determination that the treatment is safe and very effective.

Donald Trump: (07:12)
Recently, we provided up to $270 million to the American Red Cross and America's blood centers to support the collection of up to 360,000 units of plasma. In late July, we launched a nationwide campaign to ask patients who have recovered, and these are patients that have been incredible the way they've donated. But these are people recovered from the virus to donate plasma. Since then, weekly plasma donations have doubled. Today, I once again urge all Americans who have recovered from the virus to go to coronavirus.gov and sign up and donate plasma today, please. It's been really an incredible … Just incredible people. The country has united so strongly behind this.

Donald Trump: (08:08)
I'll go over the numbers, but if you look at what's happened and the success that we've had that people don't talk about, the United States has experienced the lowest case fatality rate of any major country in the world. You don't hear that. The European Union's case fatality

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rate is estimated to be three times higher than that in the United States. Europe has seen 33% more fatalities compared to a typical non-pandemic year than the United States.

Donald Trump: (08:38)
I just want to ask two of our people that have done such a fantastic job, Alex Azar and Stephen Hahn to say a few words. Stephen, I want to thank you because the FDA really stepped up and especially over the last few days in getting this done. The results have been incredible, and I think you'll see the results even go up very substantially. So we appreciate it. And maybe I'll ask Alex to go first, and then Stephen. Thank you very much, Alex.

Alex Azar: (09:06)
Well, thank you very much, Mr. President. Thanks for the bold leadership that allowed us to deliver this very happy news today. Thanks to your all-of-America approach, America has done more than any other country to expand the arsenal that we have to battle COVID-19. Thanks to early efforts by your administration, Americans have broader access to these treatments, including convalescent plasma, than patients anywhere else in the world.

Alex Azar: (09:33)
In early April, early in our fight against COVID-19, the FDA, BARDA, the Mayo Clinic, and other partners sprang into action to set up an expanded access protocol for this promising treatment. President Trump is the right-to-try President, and he's fought hard to ensure that Americans can have access to promising COVID-19 treatments. Convalescent plasma has been a tried-and-true therapeutic method in prior outbreaks, but the President wanted to ensure that we develop the data to support its use. This FDA authorization is one result of that effort.

Alex Azar: (10:06)
The data we gathered suggests that patients who were treated early in their disease course, within three days of being diagnosed with plasma containing high levels of antibodies, benefited the most from treatment. We saw about a 35% better survival in the patients who benefited most from the treatment, which were patients under 80, who were not on artificial respiration. I just want to emphasize this point because I don't want you to gloss over this number. We dream in drug development of something like a 35% mortality reduction. This is a major advance in the treatment of patients. This is a major advance.

Alex Azar: (10:51)
Convalescent plasma is one new tool that we've added to our arsenal against COVID-19 alongside remdesivir, steroids, and a number of other promising options currently being studied. Because of the President's Operation Warp Speed, we expect to have other new results and new options reaching patients as soon as this fall. Operation Warp Speed is supporting experimental therapeutics all the way through to manufacturing, so that if they meet FDA's gold standard for safety and efficacy, they can begin reaching patients without a day wasted.

Alex Azar: (11:24)
Americans who have tested positive for and recovered from COVID-19 can go to coronavirus.gov to find out a quick, convenient way to play a potentially lifesaving role in our fight. Know if you donate plasma, you could save a life. We've also provided guidance, so healthcare providers can contact patients who have recovered from COVID-19 and give them information on how they can donate.

Alex Azar: (11:48)
So thank you again, Mr. President for supporting this remarkable progress against COVID-19, and I want to thank Dr. Hahn, Dr. Marks, and the entire team at the FDA for the speed

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with which they've approached this, the diligence to ensure that this meets the standards at FDA. I'll turn it over to Dr. Hahn, if it's okay, Mr. President.

Donald Trump: (12:07)
[crosstalk 00:12:07] thank you very much. Please, Doctor?

Dr. Hahn: (12:09)
Thank you, Mr. President-

Donald Trump: (12:10)
[crosstalk 00:12:10].

Dr. Hahn: (12:10)
… for your leadership. It's good to be here today to announce FDA's recent decision. From the beginning of this pandemic, the President has asked FDA to cut back red tape to try to speed medical products into the hands of providers, patients, and American consumers. I just want to echo the President's thanks to the more than the 17,000 men and women who work at FDA. They have worked day and night to, in fact, do that.

Dr. Hahn: (12:36)
Plasma is the liquid portion of the blood. That liquid portion contains the natural immunity that someone develops in response to an infection, in this case COVID-19. That liquid portion can be extracted. And for many years, as the President and Secretary Azar said, has been given to patients with infectious diseases for more than a hundred years. So there was a really good rationale for why this might work. In fact, as was mentioned, in early April, an expanded access program was started at the Mayo Clinic with the support of the federal government under President Trump's leadership. That has gone on for the last four months. More than 90,000, close to 100,000, Americans have enrolled in this program, and over 70,000 have received treatment. This is one of the largest expanded access programs in the history of FDA. So a very successful approach to evaluating how convalescent plasma would work.

Dr. Hahn: (13:34)
In the independent judgment of experts and expert scientists at FDA who have reviewed the totality of data, not just the data from this expanded access program, but more than a dozen published studies, as well as the historical experience associated with this, those scientists have concluded that COVID-19 convalescent plasma is safe and shows promising efficacy, thereby meeting the criteria for an emergency use authorization. In the optimal patients, as described by secretary Azar, treated with convalescent plasma at the highest titers, there was a 35% improvement in survival, which is a significant clinical benefit. Now, we're waiting for more data. We're going to continue to gather data, but this clearly meets the criteria that we've established for emergency use authorization, and we're very pleased with these results.

Dr. Hahn: (14:27)
Let me just put this in perspective. Many of you know I was a cancer doctor before I became FDA commissioner, and a 35% improvement in survival is a pretty substantial clinical benefit. What that means is, and if the data continue to pan out, 100 people who are sick with COVID-19, 35 would have been saved because of the administration of plasma. We've seen a great deal of demand for this from doctors around the country. What this emergency use authorization today does, it allows us to continue that and meet the demand.

Dr. Hahn: (15:00)
Again, I want to echo the President's and the Secretary's ask of the American people. If you've recovered from COVID-19, please donate. It could save a life. Mr. President, thank you again.

Donald Trump: (15:11)
Thank you very much, Stephen. I appreciate it.

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Speaker 6: (15:18)
Mr. President?

Donald Trump: (15:19)
Okay, any questions?

Speaker 6: (15:19)
Mr. President? Mr. President?

Speaker 7: (15:19)
Thank you, Mr. President. I want to first ask you about the COVID-19 drugs that are in phase three.

Donald Trump: (15:23)
[crosstalk 00:15:24].

Speaker 7: (15:24)
Are they going to be available to the American population on … You and I talked previously about this idea of right to try.

Donald Trump: (15:32)
Right.

Speaker 7: (15:33)
Can we assure the American people that if it's being studied and it's in phase three, you have that right?

Donald Trump: (15:38)
That's a great question, and I'm not sure a lot of people have been thinking about right to try. We're all waiting for the final answer. Maybe I could ask Stephen, but I would say that right to try is exactly … If somebody is virtually terminal, in other words they're not going to make it, and if we have these incredible therapies and drugs that are happening, Alex, I think it's a very interesting question. I congratulate you for that question because I think we're-

Speaker 7: (16:05)
Thanks, Mr. President.

Donald Trump: (16:05)
… all waiting for that exact final endpoint. What about that, Stephen? We have all of these seemingly great answers that are ready to come out, but because of the process, it takes a little- Can we use some of this early under Right to Try? Please.

Dr. Hahn: (16:18)
So it's a really good question. Of course, it all depends on the clinical circumstances and what a doctor and a patient together decide with respect to the administration of any agent.

Dr. Hahn: (16:29)
But if you think about what happened with convalescent plasma and the expanded access program, this is exactly what happened. We have ongoing clinical trials that are randomized between placebo or an inactive substance and the convalescent plasma. While that was going on, we knew that there was great demand from patients and doctors. The expanded access program is a way of actually doing that and fits perfectly with what the President just said about allowing people to be able to use something that **we have now determined to be very safe.**

Donald Trump: (16:57)
I think it was something we have to really consider very strongly.

Dr. Hahn: (17:00)
Yes, sir.

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Donald Trump: (17:00)
I think it's fantastic. You should get credit for that.

Speaker 7: (17:04)
Thanks, Mr. President.

Donald Trump: (17:04)
Thank you. That's very good.

Speaker 8: (17:04)
Mr. President?

Donald Trump: (17:04)
Please, in the back. [OEN 00:17:08]?

Speaker 9: (17:10)
Thank you Mr. President. Convalescent plasma as a treatment has been around for nearly a hundred years. You mentioned Operation Warp Speed, which enabled this process to move along a lot faster. What went into the effort for this to be approved for COVID-19? And was that holdup political in nature?

Donald Trump: (17:30)
Well, I think that there might have been a holdup, but we broke the logjam over the last week, to be honest. I think that there are people in the FDA and actually in your larger department that can see things being held up and wouldn't mind so much. That's my opinion, a very strong opinion. And that's for political reasons. This has nothing to do with politics. This has to do with life or death. So we are being very strong, and we are being very forthright. We have got some incredible answers, and we're not going to let them be held up because every day is lives, and we're not going to let that happen. Okay? Very good, thank you.

Speaker 10: (18:06)
Mr. President?

Donald Trump: (18:06)
Please, go ahead.

Speaker 11: (18:10)
Mr. President, in announcing this today, you said that the FDA has made the independent determination that the treatment is **safe** and very effective. Yet Dr Hahn just said it was showing promising efficacy. Which of the two is correct?

Donald Trump: (18:25)
Well, I think I'll let Dr. Hahn answer that question.

Dr. Hahn: (18:29)
Under our legal authority for Emergency Use Authorization, this is not the same as an approval, but it's an authorization, and it allows us to expand the access to this. We know we're going to continue to collect data. We knew that for all of our Emergency Use Authorizations.

Dr. Hahn: (18:44)
So, for example, remdesivir, which was approved or authorized on May 1st, we're still collecting data, and we will continue to do that with plasma as well. So it's the nuances of the language around the authorization that we use and the legal aspect too.

Speaker 11: (18:57)
It's a promising treatment. You couldn't say it's very effective just yet.

Dr. Hahn: (19:02)
If you're one of those 35 out of 100 people who these data suggest or show survive as a result of it, this is pretty significant for that person and their family.

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Donald Trump: (19:12)
Okay, this is a very big day. It's a day we've been looking forward to. Thank you very much. Great questions.

Speaker 12: (19:18)
Was there pressure on you, Dr. Hahn, to authorize this?

Speaker 13: (19:18)
Dr. Hahn?

Speaker 14: (19:18)
Mr. President [crosstalk 00:19:19]

Speaker 12: (19:19)
Dr. Hahn. Could you answer that question? [crosstalk 00:19:19] Dr. Hahn, to authorize this.

Speaker 12: (19:21)
(silence)

552) 2020-08-23 Hahn S: Dr. Hahn discussing convalescent plasma at White House News conference. https://www.facebook.com/FDA/videos/dr-hahn-convalescent-plasma-eua/350991072605290/ goes directly to Dr. Hahn - Convalescent Plasma EUA (facebook.com) (https://www.facebook.com/FDA/videos/350991072605290/) Dr. Hahn's words that follow are extremely important because of what resulted:

> By stating that the data was not just from the Mayo Clinic/(FDA) expanded access program as you will note below, Dr. Hahn justified that the issuing of the EUA was completely appropriate. But, in so doing, availability of COVID-19 convalescent plasma from any of the previous Expanded Access Programs was now *de facto* completely suspended / interrupted.

So, in the independent judgment of experts and expert scientists at FDA, who have reviewed the totality of data – not just the data from this expanded access program but more than a dozen published studies as well as the historical experience associated with this – those scientists have concluded that COVID-19 convalescent plasma is safe and shows promising efficacy thereby meeting the criteria for an emergency use authorization.

553) 2020-08-23 Hinton DM: U.S. Food & Drug Administration Emergency Utilization Authorization (EUA) Letter to Robert P. Kadlec, MD, MTM&H, MS, Assistant Secretary for Preparedness and Response, issuing the EUA on COVID-19 Convalescent Plasma, August 23, 2020.
https://web.archive.org/web/20200823220439/https://www.fda.gov/media/141477/download

Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease. COVID-19 convalescent plasma units containing antibodies to SARS-CoV-2 but not qualified as high-titer by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units and are acceptable for use based on an individual assessment of patient benefit-risk….

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554) 2020-08-23 FDA News Release: FDA issues emergency use authorization for Convalescent Plasma as potential promising COVID-19 treatment, another achievement in Administration's fight against pandemic. U.S. Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency's ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Today's action follows the FDA's extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.
The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:
"The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Secretary Azar. "The Trump Administration recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private partners began work on making this product available across the country while continuing to evaluate data through clinical trials. Our work on convalescent plasma has delivered broader access to the product than is available in any other country and reached more than 70,000 American patients so far. We are deeply grateful to Americans who have already donated and encourage individuals who have recovered from COVID-19 to consider donating convalescent plasma."

Stephen M. Hahn, M.D., FDA Commissioner:
"I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as possible in order to save lives. We're encouraged by the early promising data that we've seen about convalescent plasma. The data from studies conducted this year shows that plasma from patients who've recovered from COVID-19 has the potential to help treat those who are suffering from the effects of getting this terrible virus," said Dr. Hahn. "At the same time, we will continue to work with researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent plasma in treating patients infected with the novel coronavirus."

Scientific Evidence on Convalescent Plasma

Based on an evaluation of the EUA criteria and the totality of the available scientific evidence, the FDA's Center for Biologics Evaluation and Research determined that the statutory criteria for issuing an EUA criteria were met.

The FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that that there are no adequate, approved, and available alternative treatments.

The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of patients into any of the ongoing randomized clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet represent a new standard of care based on the current available evidence.

The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.

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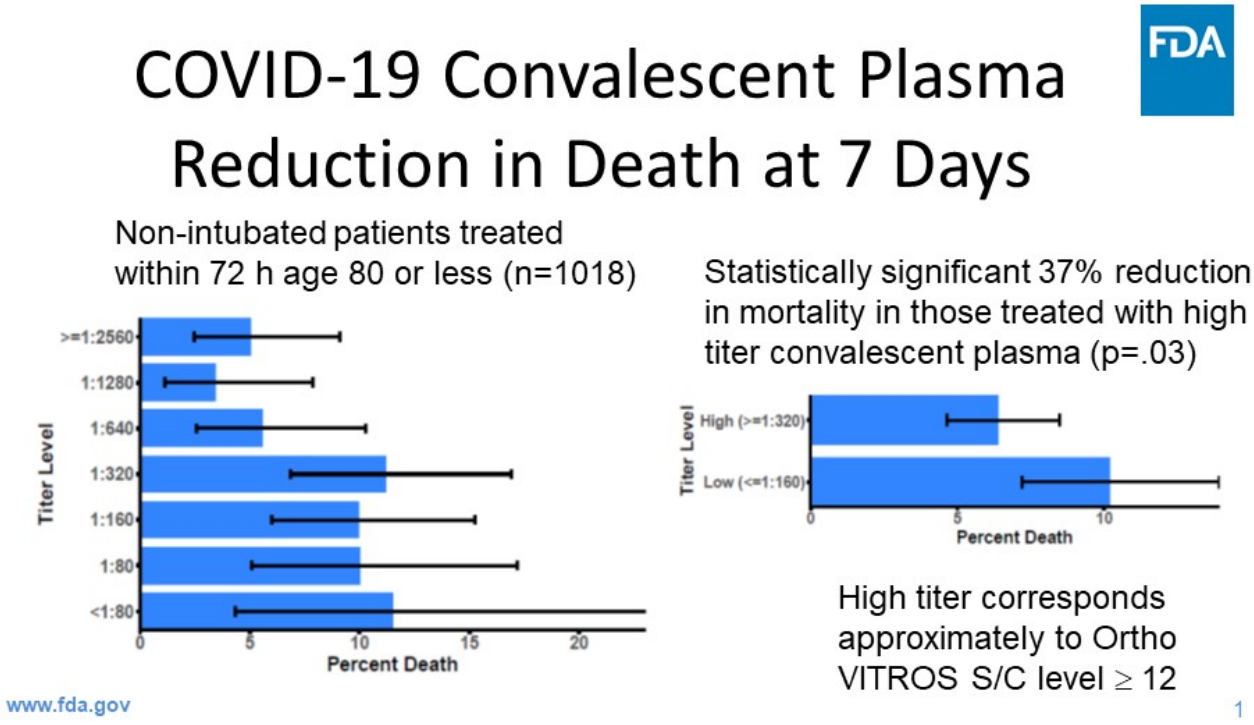

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products

555) 2020-08-23 U.S. Food & Drug Administration: Clinical Memorandum. COVID-19 Convalescent Plasma EUA Decision Memo. https://www.fda.gov/media/141480/download is the baseline URL which when placed in the Wayback Machine, 8-23-2020 to 2-2021 is the same memo on CCP EUA issued 8-23-2020: https://web.archive.org/web/20200823223716/https://www.fda.gov/media/141480/download

556) 2020-08-23 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. August 23, 2020. https://web.archive.org/web/20200901081726/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

557) 2020-08-23 U.S. Food & Drug Administration: Donate COVID-19 Plasma. http://web.archive.org/web/20201021220421/https:/www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma

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558) 2020-08-23 Gallagher C: Expanded access program for convalescent plasma discontinues enrollment as FDA authorizes its emergency use. Mayo Clinic News Network, August 23, 2020. https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/

559) 2020-08-23 Andrus CH: Re: Thousands of Americans are *needless dying* because the FDA is illegally ignoring PL 115-176 – The *Right to Try Law*[1,2] and COVID-19 Convalescent Plasma has NOT been given as Prophylaxis and Early after COVID-19 positivity conversion**. Letter mailed to President Trump and the offices of the U.S. Senate.** [In the attached CD: 06 Appendices A-H copy/01 Dear Members of Congress and President Trump 8_23_2020]

560) 2020-08-24 Thomas K, Fink S: F.D.A. 'Grossly misrepresented' blood plasma data, Scientists say. Many experts—including a scientist who worked on the Mayo Clinic study—were bewildered about where a key statistic came from. *The New York Times* Katiehttps://web.archive.org/web/20200825025014/https://www.nytimes.com/2020/08/24/health/fda-blood-plasma.html

561) 2020-08-24 Navarro P: Peter Navarro speaks with reports the day after the EUA announcement regarding COVID-19 Convalescent Plasma. https://www.c-span.org/video/?475057-101/peter-navarro-speaks-reporters

> …kinds of successes he has last thing I want to do is talk a little bit about this cot convalescent plasma this is a great thing for the American people cob lesson plasma can reduce the mortality rate by 35 percent 35 percent and. If you see controversy in the news. You should think about this. There should absolutely be no controversy about convalescent plasma this is a therapy that's been used across many diseases for many decades the odds of it. Hurting you are close to 0 the odds of it helping you are close to 100 percent the only issue is how much it can help and according to the f.d.a. a 35 percent reduction in mortality so for me this convalescent plasma debate is in some sense a litmus test if you see anybody on c.n.n. or m s n b c or in the Democratic Party question the f.d.a. decision in any way all they are doing is politicizing this issue and at a cost of American lives we cannot afford in this China virus debate to politicize or therapeutics in convalescent class by me if that's like going after Bambi you know this is the most one of the it's proven safe and effective Thank you all right. I'm a huge. Moment. For. You.
>
> Is late in our judgment where we've been trying to do this for weeks simply with. I'm not I'm not I'm not privy to what the decisions were and what the data there was I haven't looked at that but I can I again I tell you this convalescent plasma is not on controversial it's been used for decades across many diseases. The odds of it hurting you are close to 0 the odds of it helping you are close to 100 percent this is the right to try president this is a time when Americans are dying and this is something that can be useful and so so look this timing issue again I think I think it's a way of people trying to politicize what shouldn't be politicized…

562) 2020-08-25 Dockser Marcus A: Science Behind Convalescent Plasma for Covid-19 is Clouded by Politics in FDA Authorization. The Wall Street Journal Aug 25, 2020.

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https://www.wsj.com/articles/fda-officials-reject-claims-that-convalescent-plasma-decision-was-politicized-11598362563?mod=article_inline

563) 2020-08-25 Dulipsingh L, Ibrahim D, Schaefer EJ, Crowell R, Deffenderfer MR, William K, Lima C, McKenzie J, Cook L, Puff J, Onoroski M, Wakefield DB, Eadie RJ, Kleiboeker SB, Nabors P, Hussain SA: SARS-CoV-2 serology and virology trends in donors and recipients of convalescent plasma. Transfus Apher Sci 2020 Aug 25; 59: 1-6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7446657/pdf/main.pdf

564) 2020-08-26 Dasgupta A: Is a bradykinin storm brewing in COVID-19? Excess of the inflammatory molecule bradykinin may explain the fluid build-up in the lungs of patients with coronavirus infections. Clinical trials of inhibitors are putting this hypothesis to the test. TheScientist, August 26, 2020. https://www.the-scientist.com/news-opinion/is-a-bradykinin-storm-brewing-in-covid-19--67876

565) 2020-08-26 Holland S: Dr. Fauci delivers COVID-19 update at joint Grand Rounds. Office of External Affairs, Uniformed Services University, Aug 26, 2020. https://health.mil/News/Articles/2020/08/26/Dr-Fauci-delivers-COVID-19-update-at-joint-Grand-Rounds?page=6#pagingAnchor

566) 2020-08-26 HISTORY.COM Editors: Dred Scott Case. https://www.history.com/topics/black-history/dred-scott-case

567) 2020-08-28 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20200829175858/https://www.fda.gov/media/137564/download

Pages 1 – 2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)[3] for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)4 , pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers has been revised to provide updated clinical trial results and supporting data.[5] ***(VERY IMPORTANT: This negative statement: "…by no longer limiting its use to the treatment of patients with severe disease…" is obfuscation by the FDA.*** ***The positive statement that the FDA failed to state at the time and FDA has never stated is:***

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Veklury (Remdesivir) is indicated most efficaciously in the early treatment of COVID-19 in the viremic phase (best within 72 hours of diagnosis) because it inhibits RNA polymerase replication of the COVID-19 RNA. The justifying REASON for this is: "The active form of remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2. Remdesiviris incorporated by the RdRp into the growing RNA product and allows for addition of three more nucleotides before RNA synthesis stalls. …" *Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Hobartner C, Cramer P: Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nature Communicatioins (2021)12:279* https//doi.org/10.1038/s41467-020-20542-0 https://www.nature.com/articles/s41467-020-20542-0.pdf

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360 bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] The May 1, 2020 EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to add references to remdesivir's trade name, "Veklury." "Veklury" is used in this August 28, 2020 reissued letter.

[4] For purposes of the May 1, 2020 EUA, patients with severe disease were defined as patients with oxygen saturation ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

[5] Prior to this reissuance and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration

Pages 2-3:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

Distribution of the authorized Veklury will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA

> Gilead will supply Veklury to authorized distributors[7] , or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

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The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and

The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

568) 2020-08-28 Andrus CH: Re: This is a cover letter to the Congressional Staffer who will initially read the attached packet. After you read this cover letter, please bring it to your Chief of Staff so he or she might assess the importance of showing it to the Congressman or Congresswoman for whom you work. **Letter to the Offices of the U.S. House of Representatives.** [In the attached CD: 06 Appendices A-H copy/02 Dear Members of the US House of Representatives 8_28_2020]

569) 2020-09-01 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. https://web.archive.org/web/20200901081726/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma#Patient%20Eligibility

570) 2020-09-02 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. September 2, 2020. https://web.archive.org/web/20201115054330/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

571) 2020-09-02 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry. https://web.archive.org/web/20200904181318/https://www.fda.gov/media/136798/download

572) 2020-09-02 U.S. Department of Defense: Tricare Coverage of certain medical benefits in response to the COVID-19 pandemic. Regulations.gov. https://www.regulations.gov/document/DOD-2020-HA-0050-0001

573) 2020-09-03 Weixel N: White House denies Trump has embraced 'herd immunity' strategy to COVID-19. The Hill. https://thehill.com/policy/healthcare/515025-white-house-denies-trump-has-embraced-herd-immunity-strategy-to-covid

> The White House on Thursday again denied the administration has ever considered a policy of "herd immunity" for COVID-19 infections.
>
> "The herd immunity so-called theory was something made up in the fanciful minds of the media. That was never something that was ever considered here at the White House," press secretary Kayleigh McEnany told reporters during a briefing.

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McEnany was responding to reports that new White House pandemic adviser Scott Atlas, a fellow at the conservative Hoover Institution who is not an epidemiologist or infectious diseases expert, had advocated for the Trump administration to lift all restrictions aimed at stopping infections from spreading.

Atlas has publicly downplayed the importance of mask wearing, and has suggested the U.S. shouldn't be testing so many people.

The goal of herd immunity is to get as many "healthy" people infected as possible in order to build widespread resistance, while protecting the most vulnerable populations.

The U.S. has let states take the lead on their own coronavirus strategies, and there has been no centralized response from the White House. The U.S. has recorded more than 6 million COVID-19 infections and more than 186,000 deaths.

White House officials have spent the week denying The Washington Post's report that Atlas has been pushing herd immunity — and that President Trump has been listening.

Trump seemingly referred to herd immunity during an interview with Fox News on Monday.

“Once you get to a certain number, you know — we use the word herd, right?” Trump told Laura Ingraham. “Once you get to a certain number, it’s going to go away.”

On Wednesday, White House coronavirus task force coordinator Deborah Birx said she would not be a part of the administration if Trump believed herd immunity was a viable strategy.

“Neither I, nor anybody in the administration, is willing to sacrifice American lives for herd immunity. We’ll get to herd immunity through a vaccine and that’s the right way to do it,” Birx said.

Despite the denials, the administration's approach to the pandemic has changed.

- **Former deputy national security advisor: 'I think we can' find COVID-...**
- **Over 100 staff sue Houston Methodist over COVID-19 vaccine requirement**

The Centers for Disease Control and Prevention shifted its guidelines last week, and no longer recommends asymptomatic people get tested even if they have been exposed to someone with the disease.

The strategy serves to underrepresent the true number of people infected with the virus, but lower case numbers could bolster Trump's reelection chances.

Trump and his top aides have also taken to holding public events without wearing a mask and without requiring attendees to wear them, most notably last week's Republican National Convention speech on the White House lawn.

574) 2020-09-04 Root H, Bartelt L, Gilligan P: The promise of COVID-19 Convalescent Plasma Therapy. American Society for Microbiology
https://asm.org/Articles/2020/July/The-Promise-of-COVID-19-Convalescent-Plasma-Therap

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575) 2020-09-05 Martines RB, Ritter JM, Matkovic E, Gary J, Bollweg BC, Bullock H, Goldsmith CS, Silva-Flannery L, Seixas JN, Reagan-Steiner S, Uyeki T, Denison A, Bhatnagar J, Shieh W, Zaki SR, and COVID-19 Pathology Working Group: Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. CDC, Centers for Disease Control and Prevention: *Emerging Infectious Diseases.* Sept 2020; 26(9): 2005-2015. Doi: 10.3201/eid26009.202095. https://wwwnc.cdc.gov/eid/article/26/9/20-2095_article

576) 2020-09-08 Lowe D: Bradykinin and the coronavirus. https://www.science.org/content/blog-post/bradykinin-and-coronavirus

577) 2020-09-15 Simply Wall St: How much does Regeneron Pharmaceuticals' (NASDAQ:REGN) CEO make? https://simplywall.st/stocks/us/pharmaceuticals-biotech/nasdaq-regn/regeneron-pharmaceuticals/news/how-much-does-regeneron-pharmaceuticals-nasdaqregn-ceo-make

578) 2020-09-15 Kumar M, Al Khodor S: Pathophysiology and treatment strategies for COVID-19. Journal of Translational Medicine 15 Sept 2020; 18: 353- 361. https://link.springer.com/content/pdf/10.1186/s12967-020-02520-8.pdf

579) 2020-09-15 Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A, Bander J, Sanky C, Dupper A, Zheng A, Altman DR, Chen BK, Krammer F, Rao Mendu D, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM. Convalescent plasma treatment of severe COVID-19: A matched control study. medR$_X$iv preprint. Published initially on 2020 September 15 as a medR$_X$iv preprint and subsequently Nature Medicine 2020 November; 26: 1708-1713. https://www.nature.com/articles/s41591-020-1088-9.pdf

> **Abstract Results** Convalescent plasma recipients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% Cl: 0.75~0.98; p=0.028). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p = 0.039). In a covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% Cl: 0.05~0.72); p = 0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752).
>
> **Mr. President: What the abstract results above mean is that if the patients require intubation (at the end of the Cytokine Cascade and Bradykinin Storm), then there was no survival advantage to *Passive Immunization*** with COVID-19 Convalescent Plasma.--***BUT,*** if COVID-19 Convalescent Plasma was given before intubation, in all analyses in this study, there was a significant survival advantage (i.e.: all p values were < 0.05).

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580) 2020-09-16 Roth LK: Investigational COVID-19 Convalescent Plasma: Guidance for Industry; Withdrawal of guidance. U.S. Food and Drug Administration, Regulations.gov. Docket (FDA-2020-D-1825). https://www.regulations.gov/document/FDA-2020-D-1825-0011

i. *FDA is withdrawing the guidance for industry entitled "Investigational COVID-19 Convalescent Plasma" (May 2020 guidance) dated April 2020 and updated May 2020. The availability of this guidance was announced in the Federal Register of May 26, 2020, (85 FR 31513) and was posted on FDA's website on May 1, 2020.*

ii. *On August 23, 2020, the Agency issued an emergency use authorization (EUA) (available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. Given the issuance of this EUA, FDA is issuing a new guidance of the same title that provides recommendations and additional information related to the EUA for the use of COVID-19 convalescent plasma to treat hospitalized patients with COVID-19. The new guidance supersedes the May 2020 guidance. Elsewhere in this issue of the Federal Register, FDA is announcing the availability of the new guidance.*

581) 2020-09-16 European Blood Alliance: Support-E European project on COVID-19 convalescent plasma. EU Commission allocates 4M grant for SUPPORT-E. https://europeanbloodalliance.eu/activities/convalescent-plasma-cpp/support-e-european-project-on-covid-19-convalescent-plasma/

582) 2020-09-19 Altuntas F, Ata N, Yigenoglu TN, Basci S, Dal MS, Korkmaz S, Namdaroglu S, Basturk A, Hacibekiroglu T, Dogu MH, Berber I, Dal K, Kinik D, Haznedaroglu I, Yimaz FM, Kilic I, Demircioglu S, Yosunkaya A, Erkurt MA, Turgut B, Caglayan M, Celik O: Convalescent plasma therapy in patients with COVID-19. Transfusion and Apheresis Science (60) 2021. 102955 Online September 19, 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7501849/pdf/main.pdf

583) 2020-09-19 Parshley L: This theory might explain "Covid toes" and other mysteries of the disease. Vox https://www.vox.com/21445038/covid-19-symptoms-treatments-bradykinin-cytokine-storm

584) 2020-09-19 Rahaman M, Li Chen, Yao Y, Kulwa F, Rahman MA, Wang Q, Qi S, Kong F, Zhu X, Zhao X: Identification of COVID-19 samples from chest X-ray images using deep learning: A comparison of transfer learning approaches. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7592691/

585) 2020-09-20 Ibrahim D, Dulipsingh L, Zapatka L, Eadie R, Crowell R, Williams K, Wakefield DB, Cook L, Puff J, Hussain SA: Factors associationed with good patient

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Prevention: *Active Immunization*: Vaccines

outcomes following convalescent plasma in COVID-19: A prospective phase II clinical trial. Infect Dis Ther (2020) 9:913-926. https://europepmc.org/article/med/32983830

586) 2020-09-21 U.S. Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2020-D-1825]: Investigational COVID-19 Convalescent Plasma; Guidance for Industry; Availability. Federal Register / Vol. 85, No. 183 / Monday, September 21, 2020 / Notices, 59319 – 59320. https://www.govinfo.gov/content/pkg/FR-2020-09-21/pdf/2020-20801.pdf

587) 2020-09-23 Ward H: Number of annual blood plasma collections in the United States from 2007 to 2019. Statista. https://www.statista.com/statistics/756229/number-of-annual-plasma-collections-in-the-us/

588) 2020-09-23 Selvi V: Review Article: Convalescent plasma: A challenging tool to treat COVID-19 patients—A lesson from the past and new perspectives. BioMed Research International. https://downloads.hindawi.com/journals/bmri/2020/2606058.pdf

> On March 11th, 2020, the World Health Organization declared COVID-19 infection as a pandemic. Since it is a novel virus, there are basically no proven drugs or therapies; although many laboratories in different countries are working to develop a vaccine, it will take time to make it available. Passive immunization is the therapy born from the intuition of Behring and Kisato in the late 19th century. It was widely used for the treatment of bacterial infections until the discovery of antibiotics, as well as during the viral pandemics of the 20th century and of the beginning of the 21st; it still has clinical applications (e.g., tetanus prevention). This paper summarizes the basic principles of passive immunization, with particular reference to convalescent plasma. The literature concerning its use during past epidemics and the results of the first clinical studies concerning its use during the current pandemic are discussed too. A large section is dedicated to the analysis of the possible, although rare, side effects. Recently, in 2017, the WHO Blood Regulators Network (BRN) published a position paper, recommending convalescent plasma as the first choice treatment to be tested in the absence of authorized drugs; however, this strategy has not been followed. In the current epidemic, the principle of passive immunization through convalescent plasma has been applied in several circumstances and particularly in patients with serious complications. The first reported results are encouraging and confirm the effectiveness of plasma therapy and its safety. Also, the FDA has proposed plasma treatment in order to face the increasingly complex situation and manage patients with serious or immediately life-threatening COVID-19 disease. Several studies and clinical programs are still ongoing.

589) 2020-09-23 Boehmer TK, DeVies J, Caruso E, van Santen KL, Tang S, Black CL, Hartnett KP, Kite-Powel A, Dietz S, Lorzier M, Cundlapalli AV: Changing age distribution of the COVID-19 Pandemic—United States, May-August 2020. Morbidity and Mortality Weekly Report, Centers for Disease Control, U.S. Department of Health and Human Services. https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6939e1-H.pdf

590) 2020-09-23 Fara A, Miltrev Z, Rosalia RA, Assas BM: Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. The Royal Society publishing – Open Biology. 2020 Sep 23; 10(9): 200160. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7536084/

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591) 2020-09-25 Parasher A: COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2021;97:312-320. https://pmj.bmj.com/content/postgradmedj/97/1147/312.full.pdf

592) 2020-09-25 Pau AK, Aberg J, Baker J, Baker J, Belperio PS, Coopersmith C, Crew P, Grund B, Gulick RM, Harrison C, Kim A, Lane C, Masur H, Sheikh V, Singh K, Yazdany J, Tebas P, for the National Institutes of Health COVID-19 Treatment Guidelines Panel*: Convalescent plasma for the treatment of COVID-19: Perspectives of the National Institutes of Health COVID-19 Treatment Guidelines Panel. Ann of Internal Med 2021 Jan; 174 (1): 93-95. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7556653/pdf/aim-olf-M206448.pdf
This article was published at Annals.org on 25 September 2020, * For members of the National Institutes of Health COVID-19 Treatment Guidelines Panel, see the Appendix Table (available at Annals.org). ***[This is such an important article that it has been copied and pasted to follow in its entirety. This is the NIH's justification of merging Phase I (safety) trials with Phase II (efficacy) trials so as to circumvent completely ever applying PL-115-176: The Right to Try Law with regards to COVID-19 Convalescent Plasma but also any future investigational drug or biologic ad infinatum. This obfuscation by the NIH is tantamount to justifying repeated violations of PL-115-176 and is ethically shameful!].***

> Currently, no Food and Drug Administration (FDA)–approved therapeutics exist for coronavirus disease 2019 (COVID-19). In this context, the pandemic has put considerable pressure on health care providers to prescribe treatments despite limited information about their safety and efficacy. This pressure has exacerbated the tension between the importance of practicing evidence-based medicine and the urgency of providing access to promising therapies before their safety and efficacy are established.
>
> A strong scientific rationale and historical precedents exist for the study of passive immunotherapeutic approaches for viral infections (4). Concentrated, virus-specific immunoglobulin preparations are FDA approved for the postexposure prophylaxis of such viral infections as hepatitis B, varicella, and rabies (5). Recently, a randomized controlled trial (RCT) demonstrated the efficacy of 2 different monoclonal antibody products for treating Ebola virus disease (6).
>
> On 23 August 2020, the FDA issued an Emergency Use Authorization (EUA) for convalescent plasma for treating COVID-19 (2). An EUA does not constitute drug approval by the FDA. Rather, an EUA allows the FDA to facilitate the availability and unapproved uses of medical products during a public health emergency (3). The criteria for issuing an EUA for medical products include the following: The public health concern must be serious or life threatening; sufficient evidence must exist that the product "may be effective"; the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product; and no adequate, approved alternatives to the product are available (3).
>
> A strong scientific rationale and historical precedents exist for the study of passive immunotherapeutic approaches for viral infections (4). Concentrated, virus-specific immunoglobulin preparations are FDA approved for the postexposure prophylaxis of such viral infections as hepatitis B, varicella, and rabies (5). Recently, a randomized controlled trial (RCT)

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demonstrated the efficacy of 2 different monoclonal antibody products for treating Ebola virus disease (6).

The situation is less clear regarding the safety and efficacy of convalescent plasma, which has been used to treat viral infections from the 1918 influenza pandemic to the recent epidemics of severe acute respiratory syndrome (SARS), H1N1 influenza, Middle East respiratory syndrome, and Ebola virus disease (7–10). The only RCT demonstrating efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever (11).

Early in the COVID-19 pandemic, convalescent plasma was used in China to treat hospitalized patients with COVID-19 (7). Shortly thereafter, RCTs evaluating convalescent plasma in patients with COVID-19 began in several countries, including the United States (12). In March 2020, the FDA authorized expanded access to convalescent plasma for treating severe or life-threatening COVID-19 under individual-patient emergency Investigational New Drug applications. The Mayo Clinic's Expanded Access Program (EAP) was developed in parallel to provide broader access to convalescent plasma; however, it was not designed to generate definitive data on safety or to evaluate efficacy (13). One of the requirements for an EAP is that it not interfere with pivotal trials (14). Adequately powered RCTs of convalescent plasma in the United States have been slow to enroll patients.

Given the lack of data from properly powered RCTs, and the need to inform regulatory decision making regarding continued access to convalescent plasma, both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes. The results of the analyses were used as supporting evidence for the EUA.

The FDA analysis included 4330 patients, and donor neutralizing antibody titers were measured by the Broad Institute, using a SARS coronavirus 2 (SARS-CoV-2) neutralization assay (15). The analysis revealed no difference in 7-day mortality between the patients who received high-titer and those who received low-titer plasma in the overall population or in the subset of patients who were intubated. However, among nonintubated patients (approximately two thirds of those analyzed), 11% of those who received high-titer plasma died within 7 days of transfusion compared with 14% who received low-titer plasma ($P = 0.03$) (16). In a post hoc analysis of nonintubated patients who were younger than 80 years and treated within 72 hours of diagnosis, 7-day mortality for those who received high- versus low-titer plasma was 6.3% and 11.3%, respectively ($P = 0.0008$) (15).

A similar efficacy analysis by the Mayo Clinic included 3082 participants who had received a single unit of plasma among the 35 322 participants who had received plasma through the EAP by 4 July 2020 (17). Antibody titers were measured by using the VITROS anti–SARS-CoV-2 IgG assay (Ortho Clinical Diagnostics), and outcomes were compared among patients receiving low- (lowest 18%), medium-, and high-titer (highest 17%) plasma. After adjusting for baseline characteristics, the 30-day mortality rate was 29.1% in the low-titer group and 24.7% in the high-titer group. This difference did not reach statistical significance. The Mayo Clinic post hoc subgroup analyses also suggested a benefit of high-titer plasma in patients who received plasma within 3 days of COVID-19 diagnosis (17).

The FDA concluded that the totality of data, including additional data from small randomized trials and nonrandomized, observational, and animal studies, met the criteria for EUA issuance.

Despite clearly meeting the “may be effective” criterion for EUA issuance, the analyses of the EAP data are not sufficient to establish the efficacy or safety of convalescent plasma because of the lack of an untreated control group. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded. In addition, the EAP data may be subject to several confounders, including regional

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differences and temporal trends in COVID-19 management. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in convalescent plasma from patients who have recovered from COVID-19 are highly variable. In addition, the analyses focused on early mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. The efficacy analyses rely on a subset of EAP patients and thus represent only a fraction of patients who received plasma through the EAP (17). In this regard, additional analyses of the EAP cohort and completion of the current RCTs will be of critical importance.

Taking everything into account, the Panel has determined that currently the data are insufficient to recommend for or against convalescent plasma for treating COVID-19 (18). Prospective, well-controlled, and adequately powered RCTs are needed to determine whether convalescent plasma and other passive immunotherapies are effective and safe for COVID-19 treatment. Although providers have access to this therapy, the Panel cannot recommend it as a standard of care for treating COVID-19 at this time. This is consistent with the language of the convalescent plasma EUA Fact Sheet (19).

The COVID-19 pandemic has intensified the tension between providing rapid access to promising therapies and generating the scientific evidence needed to establish whether those therapies are safe and effective. This tension was also noted during the West African Ebola outbreak in 2014 to 2016, when several therapies, including convalescent plasma, were claimed to be of benefit. A National Academies of Sciences, Engineering, and Medicine review of that response noted that RCTs are critical during an outbreak, because they are the quickest way to identify effective therapies (20). Experience with convalescent plasma, hydroxychloroquine, and other interventions has taught us that large observational cohorts, EAPs, and EUAs can have a profound impact on our ability to conduct the properly designed RCTs necessary to provide definitive evidence of safety and efficacy. Conversely, the lack of access to large RCTs at many health care centers during the COVID-19 pandemic may exacerbate issues of equity in access to care. Expanded Access Programs continue to be an important mechanism to provide promising therapies for patients who do not otherwise have access to them (that is, through clinical trials). Balancing this tension is challenging but imperative to maintaining the ability to generate rigorous and convincing evidence during a public health crisis.

Despite the challenges of the COVID-19 pandemic, conducting well-controlled, adequately powered RCTs is possible. Two such trials, ACTT (Adaptive COVID-19 Treatment Trial) and RECOVERY (Randomized Evaluation of COVID-19 Therapy), recently demonstrated the efficacy of remdesivir and dexamethasone, respectively, for treating COVID-19 (21, 22). Collaboration and partnership among governmental agencies, industry, academia, and the public are needed to establish and carry out a robust and coordinated emergency research response, including the rapid development, deployment, and analysis of high-caliber RCTs. This approach is the quickest and most efficient way to generate the answers needed to provide the best evidence-based patient care.

593) 2020-09-26 St. Louis Regional Health Commission: History—1970s to 2000s Hospital closures threaten health care safety net. https://www.stlrhc.org/who-we-are/history/

594) 2020-09-29 Regeneron: Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients. While this detailed report by Regeneron to its investors was mentioned in the *Roche Investor Update* of 2020-09-30 https://www.roche.com/investors/updates/inv-update-2020-09-30.htm the URL of this report **has been wiped from the Internet site**: https://investor.regeneron.com/news-

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releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and but can be found in its entirety using the Internet Archive (Wayback Machine) http://web.archive.org/web/20201030083248/https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and ***This series of articles have legitimated de facto withholding of the early administration (<72 hours) of Passive Immunization to every American who tested positive going forward. Please note that the following news reports confirmed the existence of the original document:***

Carlson R: COVID-19 antibody cocktail found very effective. Precision Vaccinations, September 30, 2020. https://www.precisionvaccinations.com/covid-19-antibody-cocktail-found-very-effective

Beasley D: Regeneron says its COVID-19 treatment reduces viral levels, improves symptoms. Reuters APAC September 29, 2020, 9:16 PM. https://www.reuters.com/article/health-coronavirus-treatment-regeneron/regeneron-says-its-covid-19-treatment-reduces-viral-levels-improves-symptoms-idUSKBN26L08A

CNBC: Regeneron says its coronavirus treatment reduces viral levels, improves symptoms. Published Tue, Sep 29 2020, 4:19; Updated Tue, Sep 29, 2020, 4:41 PM. https://www.cnbc.com/2020/09/29/regeneron-says-its-covid-19-treatment-reduces-viral-levels-improves-symptoms.html

World Pharma Today: Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients. https://www.worldpharmatoday.com/news/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and-improved-symptoms-in-non-hospitalized-covid-19-patients-2/ The hyperlink contained within this site contains the *verbatim* copy of the missing Regeneron announcement that was accessed by the Wayback Machine above. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and; attached to this is another URL that summarized the outcomes: https://c19regn.com/regeneron.html with the graphic interpretation recorded as 5/12/2021(today) of the outcomes: https://c19regn.com/r

September 29, 2020 at 4:01 PM EDT

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REGENERON'S REGN-COV2 ANTIBODY COCKTAIL REDUCED VIRAL LEVELS AND IMPROVED SYMPTOMS IN NON-HOSPITALIZED COVID-19 PATIENTS

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TARRYTOWN, N.Y., Sept. 29, 2020 /PRNewswire/ --

Greatest improvements in patients who had not mounted their own effective immune response prior to treatment

Plan rapidly to discuss results with regulatory authorities

Regeneron to host investor and media webcast to discuss results at 4:30 pm ET today

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced the first data from a descriptive analysis of **a seamless Phase 1/2/3 trial** of its investigational antibody cocktail REGN-COV2 showing it reduced viral load and the time to alleviate symptoms in non-hospitalized patients with COVID-19. REGN-COV2 also showed positive trends in reducing medical visits. The ongoing, randomized, double-blind trial measures the effect of adding REGN-COV2 to usual standard-of-care, compared to adding placebo to standard-of-care.

This trial is part of a larger program that also includes studies of REGN-COV2 for the treatment of hospitalized patients, and for prevention of infection in people who have been exposed to COVID-19 patients.

"After months of incredibly hard work by our talented team, we are extremely gratified to see that Regeneron's antibody cocktail REGN-COV2 rapidly reduced viral load and associated symptoms in infected COVID-19 patients," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "The greatest treatment benefit was in patients who had not mounted their own effective immune response, suggesting that REGN-COV2 could provide a therapeutic substitute for the naturally-occurring immune response. These patients were less likely to clear the virus on their own, and were at greater risk for prolonged symptoms. We are highly encouraged by the robust and consistent nature of these initial data, as well as the emerging well-tolerated safety profile, and we have begun discussing our findings with regulatory authorities while continuing our ongoing trials. In addition to having positive implications for REGN-COV2 trials and those of other antibody therapies, these data also support the promise of vaccines targeting the SARS-CoV-2 spike protein."

The descriptive analysis included the first 275 patients enrolled in the trial and was designed to evaluate anti-viral activity with REGN-COV2 and identify patients most likely to benefit from treatment; the next cohort, which could be used to rapidly and prospectively confirm these results, has already been enrolled. Patients in the trial were randomized 1:1:1 to receive a one-time infusion of 8 grams of REGN-COV2 (high dose), 2.4 grams of REGN-COV2 (low dose) or placebo. All patients entering the trial had laboratory-confirmed COVID-19 that was being treated in the outpatient setting. Patients were prospectively characterized prior to treatment by serology tests to see if they had already generated antiviral antibodies on their own and were classified as seronegative (no measurable antiviral antibodies) or seropositive (measurable antiviral antibodies). Approximately 45% of patients were seropositive, 41% were seronegative and 14% were categorized as "other" due to unclear or unknown serology status.

595) 2020-09-30 Johnson CY: These laboratory-made antibodies are a best bet for a coronavirus treatment, but there won't be enough. The Washington Post https://www.washingtonpost.com/health/2020/09/30/monoclonal-antibodies-to-treat-covid-19/

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596) 2020-10 Behrns KE, Wexner SD: Times are changing and so is *Surgery*. Drs. Behrns and Wexner are the editors-in-chief. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489221/

597) 2020-10 Abasaeed Elhag S, Ibrahim H, Abdelhadi S: Angioedema and urticaria in a COVID-19 patient: A case report and review of the literature. JAAD Case Reports 2020 October; 6(10): 1091-1094. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7403866/pdf/main.pdf

> A plausible explanation for the development of angioedema lies in the established **correlation between SARS-CoV-2 and** angiotensin-converting exzyme **2, a receptor** for the virus to enter the epithelial cells of the lungs. It is known that angiotensin-converting enzyme-2 has a crucial role in the inhibition of des-ARG9 bradykinin, which is a potent ligand of bradykinin receptor 1. Hence, the inhibition of angiotensin-converting enzyme 2 has a crucial role in the inhibition of angiotensin-converting enzyme 2 leads to excessive activation of the bradykinin pathway, and subsequently increases vascular permeability leading to angioedema. This is similar to the proposed mechanism by which this virus causes acute pulmonary edema and acute respiratory distress.

598) 2020-10 Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, Xia X, Lv T: Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Me Virol. 2020; 92: 1890-1901. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25882

599) 2020-10-01 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. http://web.archive.org/web/20201015193426/https://www.fda.gov/media/137564/download

600) 2020-10-01 Farag YMK: Letter to the Editor: Limitations of safety update on convalescent plasma transfusion in COVID-19 patients. Mayo Clin Proc 2020 Dec; 95(12): 2801-2802. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7528833/pdf/main.pdf

601) 2020-10-01 Joyner MJ, Senefeld JW, Klassen SA, Fairweather D, Wright RS: In Reply – Limitations of safety update on convalescent plasma transfusion in COVID-19 patients. Mayo Clinic Proc 2020 Dec; 95 (12): 2801-2803. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7528832/pdf/main.pdf

602) 2020-10-02 Homer M: Timeline: What we know about Regeneron"s antibody cocktail that was given to President Trump. https://www.khou.com/article/news/health/coronavirus/trump-regeneron-polyclonal-antibody-cocktail/285-636b1f14-fed2-42f3-8b41-0a565a2dd967

> They are "a real best chance of being a game changer," NIH Director Francis S. Collins told the Washington Post about the experimental drug.

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603) 2020-10-05 Philippidis A, LeMieux J: Trump's treatments: Regeneron's antibodies and Gilead's Remdesivir explained. Genetic Engineering & Biotechnology News. https://www.genengnews.com/insights/trumps-treatments-regenerons-antibodies-and-gileads-remdesivir-explained/

604) 2020-10-05 LaMonica PR: Trump has ties to drugmaker Regeneron – and now its stock is surging. CNN Business https://www.cnn.com/2020/10/05/investing/trump-regeneron/index.html

> **New York (CNN Business)**President Trump received a high dose of an experimental antibody cocktail from Regeneron as part of his Covid-19 treatment. Now the drugmaker's stock is up sharply -- and questions are swirling about the president's ties to Regeneron's billionaire CEO.
>
> Trump's team revealed Friday that the president received the drug, called REGN-COV2, which is being used to alleviate symptoms and reduce viral load. Shares of Regeneron surged 7% Monday, bringing the stock's year-to-date gain to more than 60%. The stock reached its highs of the day after Trump tweeted that he will be leaving the hospital Monday evening.
> Regeneron CEO Dr. Leonard Schleifer and President Trump are acquainted: The CEO has been a member at Trump's golf club in Westchester, New York, and his company also received $450 million in government funding in July as part of the president's Operation Warp Speed plan to quickly develop a vaccine and other treatments for Covid-19.
> Meanwhile, Trump also recently owned shares of Regeneron (REGN) -- as well as Gilead Sciences (GILD), maker of the antiviral drug remdesivir that the president is also taking. Both stocks were listed as assets on Trump's 2017 filing with the U.S. Office of Government Ethics, though neither were holdings on the president's most recent filing for 2020.
> "Len and President Trump are acquaintances from both living in the Westchester area for many years but didn't have any regular contact until this year, when they've discussed matters around Covid on occasion," Regeneron told CNN Business in a statement.
> According to Forbes, Schleifer is now worth $2.5 billion, up from $2.1 billion in the middle of March. Schleifer primarily donated to Democratic political candidates and PACs in the 2016 and 2018 elections, according to Federal Election Commission records.
> Regeneron is one of many biotechs and Big Pharma firms that has skyrocketed on hopes that it may be able to quickly develop an effective coronavirus treatment. The company started human trials for its antibody cocktail in June and began a phase 3 trial just a month later.
> It has not yet been approved by the Food and Drug Administration, however. The FDA can approve the administration of it through so-called compassionate use requests on an individual basis. Regeneron confirmed to CNN Business that one of the president's doctors made such a request to Regeneron and the FDA to approve administering the drug to Trump.
>
> Schleifer defended the decision to give Trump the cocktail last week, telling CNN's Wolf Blitzer that Trump "is in a higher-risk group for a variety of reasons" and that "we hope that we will give his immune system enough of a boost so that he can win this and make a complete recovery."
> "We've got a lot of data, but we're still in the experimental phase. But when you're in the midst of a pandemic and you have people at risk, we think it makes sense to try these," Schleifer added.
> Regeneron added in its statement to CNN Business that it is "in discussions with the FDA about potential for an Emergency Use Authorization for REGN-COV2" following the release of positive data about the drug last week.
> The company had announced just a few days before President Trump's admission to Walter Reed that its cocktail "reduced viral load and the time to alleviate symptoms in non-hospitalized patients."

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Regeneron said it is also in the process of studying the effect of the cocktail on hospitalized patients, as well as whether it can prevent infection in people who have been exposed to Covid-19. Dr. George Yancopoulos, Regeneron's president and chief scientific officer, told CNN's Julia Chatterley in an interview Monday that the company is hoping it can get more doses of REGN-COV2 to patients within the next few months thanks to a partnership with Big Pharma giant Roche.
"We are on track to deliver 300,000 doses by the end of the year and...produce 300,000 doses a month while the demand may even still exceed that," Yancopoulos said. "If the drug is really working and having the effects that we all hope it would, it could be doing a lot of good for a lot of people."
Correction: An earlier version of this story misstated the compassionate use request process. One of the president's physicians made the request to Regeneron and the FDA.

605) 2020-10-05 Cohen J: Update: Here's what is known about Trump's COVID-19 treatment. Science https://www.sciencemag.org/news/2020/10/heres-what-known-about-president-donald-trump-s-covid-19-treatment

606) 2020-10-05 Gringlas S, Sprunt B: Timeline: What we know of President trump's COVID-19 diagnosis, treatment. NPR. https://www.npr.org/sections/latest-updates-trump-covid-19-results/2020/10/03/919898777/timeline-what-we-know-of-president-trumps-covid-19-diagnosis

607) 2020-10-05 Wilt TJ, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter: Remdesivir for Adults with COVID-19—A living systematic review for an American College of Physicians Practice Points. Ann Internal Med, Published at Annals.org on 5 October 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7564604/pdf/aim-olf-M205752.pdf

*[**Mr. President, the VA DID NOT EVEN READ its own publications**! One month after this publication (the abstract is pasted below) and after Velkury (remdesivir) was approved by the FDA on October 22, 2020 as the **only licensed** drug to this day in the treatment of COVID-19: NDA #21478, the VA Central Office issued **Remdesivir (VELKURY) Criteria for Use, November 2020** limiting use of Velkury (remdesivir) to only: "**Inclusion Criteria, The following must be fulfilled in order to meet the criteria for remdesivir**: Hospitalized with **SEVERE** COVID-19 [room air oxygen saturation <94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO]*** "] In December e-mail discussions* (see Appendices E of this correspondence) *with Richard Stone, M.D., former VHA Chief Medical Executive (former Acting VHA Undersecretary for Health during the early part of your administration), I pointed out this **Significant Directive Error** to Dr. Stone as well as the FDA, the NIH, and the Editors of The New England Journal of Medicine.* THIS INCORRECT DIRECTIVE of VA policy CONTINUES EVEN TO THIS DAY, AUGUST 5, 2021, and is ACCESSIBLE ON THE INTERNET as VA policy.*]* Also, please note the FDA removed the erroneous administration criteria from all its publications on August 28, 2020 and RADM Hinton, FDA Chief Scientist, encouraged **early administration of remdesivir (COVID-19 viremic phase)** in the individual patient after COVID-19 laboratory confirmation in the asymptomatic state and forward.

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Annals of Internal Medicine REVIEW

Remdesivir for Adults With COVID-19

A Living Systematic Review for an American College of Physicians Practice Points

Timothy J. Wilt, MD, MPH; Anjum S. Kaka, MD; Roderick MacDonald, MS; Nancy Greer, PhD; Adam Obley, MD; and Wei Duan-Porter, MD, PhD

Background: Few treatments exist for coronavirus disease 2019 (COVID-19).

Purpose: To evaluate the effectiveness and harms of remdesivir for COVID-19.

Data Sources: Several databases, tables of contents of journals, and U.S. Food and Drug Administration and company websites were searched from 1 January through 31 August 2020.

Study Selection: English-language, randomized trials of remdesivir treatments for adults with suspected or confirmed COVID-19. New evidence will be incorporated using living review methods.

Data Extraction: Single-reviewer abstraction and risk-of-bias assessment verified by a second reviewer; GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods used for certainty-of-evidence assessments.

Data Synthesis: Four randomized trials were included. In adults with severe COVID-19, remdesivir compared with placebo probably improves recovery by a large amount (absolute risk difference [ARD] range, 7% to 10%) and may result in a small reduction in mortality (ARD range, -4% to 1%) and a shorter time to recovery or clinical improvement. Remdesivir may have little to no effect on hospital length of stay. Remdesivir probably reduces serious adverse events by a moderate amount (ARD range, −6% to −8%). Compared with a 10-day remdesivir course, a 5-day course may reduce mortality, increase recovery or clinical improvement by small to moderate amounts, reduce time to recovery, and reduce serious adverse events among hospitalized patients not requiring mechanical ventilation. Recovery due to remdesivir may not vary by age, sex, symptom duration, or disease severity.

Limitations: Low-certainty evidence with few published trials, including 1 preliminary report and 2 open-label trials. Trials excluded pregnant women and adults with severe kidney or liver disease.

Conclusion: In hospitalized adults with COVID-19, remdesivir probably improves recovery and reduces serious adverse events and may reduce mortality and time to clinical improvement. For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide similar benefits to and fewer harms than a 10-day course.

Primary Funding Source: U.S. Department of Veterans Affairs, Veterans Health Administration Office of Research and Development, Health Services Research and Development Service, and Evidence Synthesis Program.

Ann Intern Med. doi:10.7326/M20-5752 Annals.org
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 5 October 2020.

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

☐ Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

608) 2020-10-05 McKenzie H: Could an intranasal COVID-19 vaccine be more efficient and effective than traditional approach? https://www.biospace.com/article/why-an-intranasal-covid-19-vaccine-could-be-more-efficient-and-effective/

609) 2020-10-06 Rogers TN: Meet the billionaire doctors behind Regeneron, the pharmaceutical company that developed Trump's experimental COVID-19 treatment. https://www.businessinsider.com/regeneron-billionaires-schleifer-yancopoulos-trump-covid-drug-2020-10

610) 2020-10-06 Jennings DG: Is Regeneron (NASDAQ: REGN) making money?—Market Mad House. https://marketmadhouse.com/is-regeneron-nasdaq-regn-making-money/

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611) 2020-10-07 Loftus P: Eli Lilly asks FDA to authorize Covid-19 antibody Drug. Wall Street Journal, Updated October 7, 2020, 11:31 pm ET. https://www.wsj.com/articles/eli-lilly-asks-fda-to-authorize-covid-19-antibody-drug-11602074998

> If cleared for use, the drug could be the first to treat less severe cases of Covid-19. The few other therapies authorized for Covid-19 treatment, including remdesivir from Gilead Sciences Inc. GILD 1.41% and convalescent plasma, target hospitalized patients with more serious cases.
>
> Lilly said it would seek authorization for use in higher-risk patients to prevent their recently diagnosed mild-to-moderate disease from worsening to a severe state. Executives of the Indianapolis-based company said higher-risk groups may include people 65 years of age or older or obese patients.
>
> "Anything that helps with preventing hospitalization and preventing progression is going to be a big advance," Rajesh Tim Gandhi, an infectious-disease physician at Massachusetts General Hospital and Harvard Medical School, said in an interview.
>
> Lilly's antibody drug could also be the first in a new class of Covid-19 agents that not only might provide treatment but also potentially give temporary protection against the virus to people at risk of infection. That would fill a gap until vaccines are authorized, though people may need to take the antibody drugs more than once to sustain the protection.
> "When we started this project we always believed that vaccines would be a long-term solution but that antibodies could come to patients faster," Lilly research head Daniel Skovronsky said in an interview. "We can make them faster, test them faster."
>
> The leading experimental antibody drugs have shown enough promise in testing so far that President Trump was given one developed by Regeneron Pharmaceuticals Inc.
> Regeneron said Wednesday night it has asked the Food and Drug Administration to authorize use of its antibody drug cocktail for Covid-19. The company said it has supply for 50,000 patients available and will have 300,000 within a few months.
>
> Lilly said last month its drug reduced the rate of hospitalization compared with a placebo in a study. About 1.6% were hospitalized or visited the emergency room for Covid-19 after being injected with the drug, compared with 5.8% of people who didn't get the drug in the study

612) 2020-10-07 Gumbrecht J, Howard J: Eli Lilly seeks EUA from FDA to Covid-19 antibody treatment. CNN Health. The 3 minute 42 second video attached to this article is the most succinct overview of antibody therapies that should be employed in the treatment of COVID-19 regarding both **Passive Immunization** [the early administration of exogenous neutralizing antibodies to individuals (<72 hours of COVID-19 detection or prophylactically)] and **Active Immunization** [vaccination of an individual which is prevention after the ~ 2-3 week increasing development of neutralizing antibodies in the uninfected individual). https://www.cnn.com/2020/10/07/health/eli-lilly-antibody-therapy-results-eua/index.html

613) 2020-10-08 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil A, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

DC, Ohmagari N, Oh Myoung-don, Ruiz-Palacios GM, Benfield T, Fatkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Bergess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC, for the ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 – Final Report. NEJM.org, October 8, 2020. Published in harcopy N Engl J Med 2020; 383:1813-1826. November 5, 2020. A preliminary version of this article was published on May 22, 2020. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764 .

SAFETY OUTCOMES

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group (Table S17). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients) (Table S19). No deaths were considered by the investigators to be related to treatment assignment.

Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group (Table S18); 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo (Table S17). The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level (Table S20). The incidence of these adverse events was generally similar in the remdesivir and placebo groups.

Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratory-confirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3). A variety of therapeutic approaches including novel antivirals, modifiers of the immune response or other intrinsic pathways, and combination approaches are needed to continue to improve outcomes in patients with Covid-19.

614) 2020-10-08 Beaumont P, Boseley S, Glenza J: Provider of Trump Covid drug is president's golf friend. https://www.theguardian.com/world/2020/oct/08/provider-of-trump-covid-drug-is-presidents-golf-friend

615) 2020-10-08 Hart R: While Trump touts 'Cure' made by Regeneron, Its CEO is a member of Trump golf club. October 8, 2020. https://www.forbes.com/sites/roberthart/2020/10/08/while-trump-touts-cure-made-by-regeneron-its-ceo-is-a-member-of-trump-golf-club/?sh=22fa6b7a60c8

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616) 2020-10-09 NIH—COVID-19 Treatment Guidelines – Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, Convalescent Plasma. *Last Updated: October 9,2020*, Page 102-108. https://files.covid19treatmentguidelines.nih.gov/guidelines/archive/covid19treatmentguidelines-10-09-2020.pdf

Convalescent Plasma

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.[1]

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.[2,3] Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.[4,5] Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents.[3,6,7]

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617) 2020-10-09 Hancock J: As Trump touts his 'great' COVID drugs, the pharma cash flows to Biden, not him. https://khn.org/news/trump-touts-covid-cure-regeneron-drug-pharma-political-contributions-strongly-benefit-biden/

618) 2020-10-10 BBC: White House hosted Covid 'superspreader' event, says Dr Fauci. https://www.bbc.com/news/election-us-2020-54487154

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619) 2020-10-10 Zimmermann P, Curtis N: Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Children 2020;0:1-11. https://adc.bmj.com/content/archdischild/early/2020/11/30/archdischild-2020-320338.full.pdf

620) 2020-10-11 Mack E: Regeneron CEO, a Dem Donor, rejects his treatment as 'Cure'. Newsmax https://www.newsmax.com/politics/regeneron-cure-treatment-covid/2020/10/11/id/991436/

621) 2020-10-11 O'Brien C: Regeneron CEO: Trump 'is a case of one' and 'weakness evidence' for Covid-19 treatment. Politico https://www.politico.com/news/2020/10/11/regeneron-trump-covid-coronavirus-428691

622) 2020-10-11 Smith A: Trump declares himself 'immune' to Covid-19. His doctors won't say when he last tested negative. NBC News. https://www.nbcnews.com/politics/2020-election/trump-declares-himself-immune-covid-19-his-doctors-won-t-n1242851

623) 2020-10-12 Tillett R, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, Laverdure C, Verma SC, Rossetto CC, Jackson D, Farrell MJ, van Hooser S, Pandori M: Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis 2020; 21: 52-58. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550103/pdf/main.pdf

624) 2020-10-14 Eli Lilly and Company: Lilly statement on the NIAID decision to pause enrollment in ACTIV-3 clinical trial. https://www.lilly.com/news/stories/statement-activ3-clinical-trial-covid19-niaid-decision-pause-enrollment

625) 2020-10-14 Volkman E: Eli Lilly coronavirus antibody drug trial paused—The National Institutes of Health put the brakes on the study in what the drugmaker calls "an abundance of cautions." The Motley Fool https://www.fool.com/investing/2020/10/14/eli-lilly-coronavirus-antibody-drug-trial-paused/

626) 2020-10-14 Buchanan L, Gamio L, Leatherby L, Keefe J, Koetti C, Schoenfeld Walker A: Tracking the White House Coronavirus Outbreak. The New York Times https://www.nytimes.com/interactive/2020/10/02/us/politics/trump-contact-tracing-covid.html

627) 2020-10-16 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20201017135559/https://www.fda.gov/media/137564/download

Pages 1-2:
On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)[3] for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)[4], pursuant to Section 564 of the Act.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to **expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease**. In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.[5]

> **CONTRARY TO REFERENCE #4 WHICH STATES:** "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, …"**expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."**

On October 1, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors[6] as the responsible parties for the distribution[7] of Velkury. FDA is reissuing the October 1, 2020, letter in its entirety with revisions to clarify that an alternate care site (ACS) meeting certain criteria is considered an "inpatient hospital setting" for the purposes of the scope of the EUA, and as such, is within the terms and conditions of FDA's authorization.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3,* 85 FR 18250 (April 1, 2020).

[3] The May 1, 2020, EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to addreferences to remdesivir's trade name, "Veklury." "Veklury" is used in the August 28, 2020, reissued letter.

[4] For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). (PLEASE NOTE THAT AFTER AUGUST 28, 2020 THESE "SEVERITY OF DISEASE' WERE REVOKED BY THE FDA.)

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[5] Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized ,clinical trials; (5) removed information related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.
[6] "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.
[7] Allocations of Veklury directed by the United States Government on or before September 30, 2020, remain valid and shall be distributed in collaboration with state or local government authorities, as needed.

Page 3:

3. There is no adequate, approved, and available alternative to the emergency use of Veklury for the treatment of COVID-19. 8

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

• The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an inpatient hospital setting[9] via intravenous (IV) infusion by a healthcare provider; and

• The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

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[8] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[9] Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.
[10] The product labeled "investigational use" is authorized for use under this EUA; FDA is not requiring it to be relabeled given the immediate need for the product.

628) 2020-10-19 BBC News: England boosting plasma stocks for patients. https://www.bbc.com/news/health-54597690

NHS Blood and Transplant is boosting stocks of blood plasma for very ill coronavirus patients ahead of winter.

It wants more people who have recovered from Covid-19 to become donors.

Their **plasma contains antibodies that are believed to help other sufferers** fight the virus.

Fourteen new donation centres will open in November and December, to bring the total in England to 42. The blood plasma will be used to treat patients in Covid trials.

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629) 2020-10-20 KEI Staff: Regeneron failed to disclose BARDA funding in their REGN-COV2 patent. https://www.keionline.org/34258

630) 2020-10-21 Harris R: How will the limited supply of antibody drugs for COVID-19 be allocated? NPR October 21, 2020. https://www.npr.org/sections/health-shots/2020/10/21/926376342/how-will-the-limited-supply-of-antibody-drugs-for-covid-19-be-allocated

1. BARDA funds 80 percent of the R&D related to Regeneron's COVID-19 program

Regeneron has told their investors that the BARDA "is obligated to fund 80% of our costs incurred for certain research and development activities related to COVID-19 treatments." [1] This commitment stems from the expansion of an existing contract with BARDA known as "HHSO100201700020C". [2] Contract HHSO100201700020C was first established on September 29, 2017 to discover, research, develop, and manufacture antibody treatments against Ebola, Influenza, and other pathogens. [3] On January 31, 2020, BARDA and Regeneron expanded their collaboration under the HHSO100201700020C contract to include work relating to antibodies against COVID-19. [4]

According to BARDA, the base amount awarded to Regeneron under their collaboration specifically for work related to antibodies against COVID-19 was $82,368,277. [5] Since then, Regeneron has further expanded their collaboration with the U.S. government. On July 7, 2020, the Department of Defense, through an intermediary called Advanced Technology International, awarded a $450 million contract to Regeneron, to manufacture and supply REGN-COV2. 6 The extent to which costs are shared under the $450 million contract is unknown.

As we explain in this report, the research leading to the selection of the two antibodies that comprise the REGN-COV2 cocktail was funded with the HHSO100201700020C contract.

631) 2020-10-22 Hinton DM, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury® (remdesivir) for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)[3], pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. At that time, Veklury was an investigational drug and not approved for any indication.

On August 28, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to **expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease**. In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.[4]

CONTRARY TO THE EUA PRIOR TO AUGUST 28, 2020: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

oxygenation (ECMO).", AS OF AUGUST 28, 2020, …"**expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."**

On October 1, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors[5] as the responsible parties for the distribution of Velkury. On October 16, 2020, FDA reissued the October 1, 2020, letter in its entirety with revisions to clarify that **an alternate care site (ACS) meeting certain criteria was considered an "inpatient hospital setting"** for the purposes of the scope of the EUA, and as such, was within the terms and conditions of FDA's authorization. On October 22, 2020, FDA approved NDA 214787 for Veklury (remdesivir), which is indicated for adults and pediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Under its approval, **Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.** Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the October 16, 2020, letter in its entirety with revisions to remove uses previously authorized that are now the subject of the approved NDA 214787 for Veklury, and to continue authorizing Veklury for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act,* 21 U.S.C. § 360bbb-3. February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act,* 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).

[3] For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

[4] Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized, clinical trials; (5) removed information

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related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.
[5] "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

CONTRARY TO PRIOR TO AUGUST 28, 2020: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, …"**expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."**

Page 3:

II. Scope of Authorization I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

• The Veklury covered by this authorization will be used only to treat suspected or laboratory-confirmed COVID-19 in hospitalized[7] pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg administered via intravenous (IV) infusion by a healthcare provider; and

• The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

[6] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[7] **Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care** are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.
[8] FDA's authorization includes remdesivir for injection manufactured and labeled prior to Gilead's reference to remdesivir's trade name, "Veklury", in product labeling.

ALSO, PLEASE NOTE FOOTNOTE (7) ABOVE WHICH EXPANDS THE SITES OF INFUSION FROM "ACUTE INPATIENT HOSPITAL" TO "…ARE ADMITTED OR TRANSFERRED TO AN ALTERNATE CARE SITE (ACS) THAT IS CAPABLE OF PROVIDING ACUTE CARE THAT IS COMPARABLE TO GENERAL INPATIENT HOSPITAL CARE…".

632) 2020-10-22: Farley JJ, Director, Office of Infectious Diseases, U.S. Food & Drug Administration: FDA New Drug Approval for Remdesivir **NDA 214787**. Letter from John Farley, MD, MPH to Ms Rhoades, Gilead Sciences, Inc. authorizing a **New Drug Authorization Approval**
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf

NDA APPROVAL 214787

Gilead Sciences, Inc.
Attention: Ashley Rhoades, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Rhoades:

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Prevention: *Active Immunization*: Vaccines

Please refer to your new drug application (NDA) dated and received August 7, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEKLURY (remdesivir) injection, 5 mg/mL; VEKLURY (remdesivir) for injection, 100 mg/vial.

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) **for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.**

633) 2020-10-22 U.S. Food and Drug Administration: FDA News release. FDA approves first treatment for COVID-19. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

Today, the U.S. Food and Drug Administration approved the antiviral drug Veklury (remdesivir) for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Veklury is the first treatment for COVID-19 to receive FDA approval.

This approval does not include the entire population that had been authorized to use Veklury under an Emergency Use Authorization (EUA) originally issued on May 1, 2020. In order to ensure continued access to the pediatric population previously covered under the EUA, the FDA revised the EUA for Veklury to authorize the drug's use for treatment of suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. Clinical trials assessing the safety and efficacy of Veklury in this pediatric patient population are ongoing.

"The FDA is committed to expediting the development and availability of COVID-19 treatments during this unprecedented public health emergency," said FDA Commissioner Stephen M. Hahn, M.D. "Today's approval is supported by data from multiple clinical trials that the agency has rigorously assessed and represents an important scientific milestone in the COVID-19 pandemic. As part of the FDA's Coronavirus Treatment Acceleration Program, the agency will to continue to help move new medical products to patients as soon as possible, while at the same time determining whether they are effective and if their benefits outweigh their risks."

Under the Federal Food, Drug, and Cosmetic Act, approval of a new drug product requires substantial evidence of effectiveness and a demonstration of safety for the drug's intended use(s). In considering approval of a drug, the FDA conducts a benefit-risk assessment based on rigorous scientific standards to ensure that the product's benefits outweigh its risks for the intended population. This is different from the standard used in the issuance of an EUA.

The approval of Veklury was supported by the agency's analysis of data from three randomized, controlled clinical trials that included patients hospitalized with mild-to-severe COVID-19.

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634) 2020-10-22 Gilead Sciences per FDA: Highlights of prescribing information for Veklury (Remdesivir) and FULL PRESCRIBING INFORMATION. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf

635) 2020-10-22 U.S. Food and Drug Administration: Donate COVID-19 Plasma. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma

636) 2020-10-23 Lerner S: Trump sets up pharma billionaires for coronavirus payday. Regeneron's federally funded Covid-19 treatment, which was used to treat Donald Trump, will likely be unavailable to most patients. The Intercept. ***[As is stated in the yellow area below, "Regeneron…committed…to selling some of the antibodies to the government, which in turn is obligated to distribute them 'to the American people at no cost,'" according to the government's July 6 agreement, that deal applies to 'a fixed number of bulk lots.'" That was a year ago. On April 13, 2021, it was announced that "Roche (was) taking the lead on development of the antibody cocktail outside of the U.S."[439] While REGN-COV2 is still an investigational biologic drug (monoclonal antibiotic cocktail) in the U.S. as of today, August 4, 2021, it is available to those who can obtain it in India for 59,000 Repees (~$800 U.S.)[471]]*** https://theintercept.com/2020/10/23/trump-covid-19-pharma-regeneron-coronavirus-treatment/

Shortages Expected

Hours after the president tweeted the video, in which he said that emergency use authorization for the antibody cocktail was "all set," Regeneron applied for the fast tracking, which would make the treatment available before it has been thoroughly vetted. But the Food and Drug Administration has yet to grant the authorization.

While Regeneron initially estimated that it would have between 70,000 and 300,000 doses "as early as end of summer and completed this fall," Schleifer admitted on CBS News' "Face the Nation" that, as of October 11, it had only produced 50,000 doses, which is fewer than the number of coronavirus infections diagnosed on a single day in the U.S. last week.

And although Regeneron has committed to selling some of the antibodies to the government, which in turn is obligated to distribute them "to the American people at no cost," according to the government's July 6 agreement, that deal applies only to "a fixed number of bulk lots." After that, the pricing is up to the company — a prospect that frightens some economists.

"Executives have an interest in getting the stock price up and price gouging customers is one way they can do this," said William Lazonick, professor emeritus of economics at University of Massachusetts and co-founder of the Academic-Industry Research Network. While many drug companies argue that they use their vast profits to fund ongoing pharmaceutical innovation, Lazonick said, "we've shown that most of these companies don't do that." Instead, the soaring prices fuel soaring stock prices and executive pay, which is often based largely on that price.

The pharmaceutical industry has a long history of opposing efforts to rein in drug prices, including the "affordable pricing" clause. Regeneron was fighting that measure, which obligates

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companies that develop drugs with public money to sell them at reasonable prices, as far back as 1994.

Monoclonal antibodies are already among the most expensive pharmaceutical products available. The treatments on the market for conditions other than Covid-19 cost an average of $96,731 per year. When used to treat cancer, the antibodies went for a median price of $142,833, according to a 2018 study in the American Journal of Managed Care.

A Looming Nightmare

While Trump promised that the government would provide the antibody cocktail to Americans for free, drug pricing efforts say that many people probably won't have access to the treatment at all, let alone at an affordable price.

"This is a looming nightmare," said Zain Rizvi, a drug pricing expert who works at Public Citizen. "If the drug is safe and effective, the shortages will be rampant and will exacerbate the insidious inequality that's already part of our healthcare system. The privileged few may get at the head of the line and the people who need it most may not have the same opportunities."

While Rizvi said that a lack of regulation plagues the entire U.S. pharmaceutical system, he said the maker of the antibody cocktail epitomizes the administration's failure to hold companies accountable during the pandemic. "The story of Regeneron's monoclonal antibody treatment is the story of president Trump's billionaire buddy who received massive taxpayer subsidies to work on a coronavirus treatment with no strings attached," said Rizvi, who pointed out that Regeneron will be able to both set high prices for the tax-payer funded treatment and market it exclusively. "You have massive public investment, but the knowledge that comes out of it is being privatized. It doesn't benefit public health."

Already the pandemic has showcased a brutal disparity in health care. Unlike Trump, who was given two cutting-edge treatments that are inaccessible to the general public a few days after being diagnosed, patients have often had to wait for medical care when hospitals were stretched to capacity — delays that sometimes proved deadly. Although the administration has set up a fund to help cover the costs of some coronavirus treatments, many patients do not qualify. Some survivors of the disease have been hit with staggering medical bills for their treatments. And a lack of insurance is believed to have contributed to the astronomical toll of the pandemic, which has already claimed more than 223,000 lives.

For his part, Trump announced he was feeling "like perfect" after taking the Regeneron cocktail and hurried back to the White House. Once there, he helped fast-track the confirmation process of Amy Coney Barrett, his Supreme Court nominee who is widely expected to vote to strip tens of millions of Americans of their health care coverage and to outlaw the kind of research that produced the very treatment that he claims cured him.

Meanwhile, as the virus continues to surge across the country, Regeneron has said that it is continuing to produce its monoclonal antibodies and will do its best to make the treatment available to everyone.

"We are committed to ensuring that REGN-COV2 will be affordable for patients in need," Regeneron said in its emailed statement. "We know our medicines only help if people can access them, and, as such, we are working hard to develop and scale-up a completely novel treatment for COVID-19 that is accessible to the people who need it."

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For Rizvi, the reassurance rings hollow. “The corporate executives will control the price and the supply,” he said. “What could go wrong?”

637) 2020-10-27 Regen Lab SA: Passive immune prophylaxis preventing COVID-19 with ‘Acellular-Convalescent Plasma’ (A-CP): a new technology introduced by Regen Lab®. https://www.prnewswire.com/in/news-releases/passive-immune-prophylaxis-preventing-covid-19-with-acellular-convalescent-plasma-a-cp-a-new-technology-introduced-by-regen-lab-r--807452422.html

638) 2020-10-27 Yeager A: Eli Lilly halts antibody trial in hospitalized COVID-19 patients. Recent data show that the drug bamlanivimab, also known as LY-CoV555, does not appear to help those with severe cases of COVID-19, but trials continue for milder cases. TheScientist https://www.the-scientist.com/news-opinion/eli-lilly-halts-antibody-trial-in-hospitalized-covid-19-patients-68090

639) 2020-10-28 Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM, for the BLAZER-1 Investigators. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. NEJM.org October 28, 2020; published in N Engl J Med, January 21, 2021; 384 (3): 229-237. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2029849?articleTools=true

640) 2020-10-28 Regeneron: Regeneron’s COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced virus levels and need for further medical attention. https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates

REGENERON'S COVID-19 OUTPATIENT TRIAL PROSPECTIVELY DEMONSTRATES THAT REGN-COV2 ANTIBODY COCKTAIL SIGNIFICANTLY REDUCED VIRUS LEVELS AND NEED FOR FURTHER MEDICAL ATTENTION

TARRYTOWN, N.Y., Oct. 28, 2020 /PRNewswire/ --

Today's data, involving an additional 524 patients from the ongoing Phase 2/3 trial, provides definitive final virology results and meets the clinical endpoint of reducing medical visits

Regeneron has shared these results with the U.S. FDA, which is reviewing an Emergency Use Authorization submission for the REGN-COV2 low dose in adults with mild-to-moderate COVID-19 who are at high risk for poor outcomes

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
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Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive, prospective results from **an ongoing Phase 2/3 seamless trial** in the COVID-19 outpatient setting showing its investigational antibody cocktail, REGN-COV2, met the primary and key secondary endpoints. REGN-COV2 significantly reduced viral load and patient medical visits (hospitalizations, emergency room, urgent care visits and/or physician office/telemedicine visits).

"The first job of an antiviral therapeutic drug is to lower the viral load, and our initial data in 275 patients strongly suggested that the REGN-COV2 antibody cocktail could lower viral load and thereby potentially improve clinical outcomes. Today's analysis, involving more than 500 additional patients, prospectively confirms that REGN-COV2 can indeed significantly reduce viral load and further shows that these viral reductions are associated with a significant decrease in the need for further medical attention," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "We continue to see the strongest effects in patients who are most at risk for poor outcomes due to high viral load, ineffective antibody immune response at baseline, or pre-existing risk factors. Regeneron has shared these results with the U.S. Food and Drug Administration as part of its review of our Emergency Use Authorization submission, and we continue to focus on completing our ongoing trials evaluating REGN-COV2 for the treatment and prevention of COVID-19."

The randomized, double-blind trial is measuring the effect of adding REGN-COV2 to usual standard-of-care, compared to adding placebo to standard-of-care. A descriptive analysis from the first 275 patients was previously reported. Today's data, involving an additional 524 patients, show the trial met all of the first nine endpoints in the statistical hierarchy, which assessed virologic endpoints based on viral load, seronegative status and dose group, as well as the key clinical endpoint of COVID-19 related medically-attended visits, in patients who had laboratory-confirmed COVID-19 at baseline. Results showed no significant difference in virologic or clinical efficacy between the REGN-COV2 high dose (8 grams) and low dose (2.4 grams). Based on this finding, Regeneron is reviewing potential changes to dosing in the ongoing outpatient clinical trial given the current limited supply of REGN-COV2.

Virologic results (n=524, prospectively confirming previous 275-patient analysis):

641) 2020-10-28 Lilly: Lilly announces agreement with U.S. government to supply 300,000 vials of investigational neutralizing antibody bamlanivimab (LY-CoV555) in an effort to fight COVID-19. https://investor.lilly.com/node/43881/pdf

Lilly has successfully completed a Phase 1 study of bamlanivimab in hospitalized patients with COVID-19 (https://clinicaltrials.gov/ct2/show/NCT04411628). A Phase 2 study in people recently diagnosed with COVID-19 in the ambulatory setting (BLAZE-1, https://clinicaltrials.gov/ct2/show/NCT04427501) is ongoing. A Phase 3 study of bamlanivimab for the prevention of COVID-19 in residents and staff at long-term care facilities (BLAZE-2, https://clinicaltrials.gov/ct2/show/NCT04497987) is also ongoing. In addition, bamlanivimab is being tested in the National Institutes of Health-led ACTIV-2 study of ambulatory COVID-19 patients.

Eli Lilly and company have twelve Clinical Trials posted as of June 1, 2021 on NIH https://clinicaltrials.gov and only one is listed as a Phase I trial (which was nominally completed

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on August 26, 2020). Therefore, as of August 26, 2020, Eli Lilly's monoclonal antibody (Ly-CoV555) bamlanivimab https://clinicaltrials.gov/ct2/show/NCT04411628?term=eli+lilly&cond=Covid19&draw=2&rank=4 met the criteria of the intent of PL-115-176, the Right to Try Act of 2017, which stipulates that the only requirement that must be met so that a patient can request an Investigational Drug or Biologic outside of a clinical trial is that a **Phase I clinical trial be "completed."** The nominal completion date of NCT04411628 on NIH https://clinicaltrials.gov is **August 26, 2020**. While the monoclonal antibody bamlanivimab met the criteria set forth by the FDA https://www.fda.gov/media/72057/download and by the NIH https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html for a completed **Phase I Clinical Trial**, the FDA, the NIH, and Eli Lilly failed to notify the American public, the American Medical profession, and the rest of the Federal Government that bamlanivimab should have been available to all Americans within 72 hours of documented contraction of COVID-19 from August 26, 2020 to the present at their request under PL-155-176, the Right to Try Law, https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf.

642) 2020-10-30 McGrail S: Eli Lilly strikes deal with Govt over COVID-19 antibody drug. HHS and DoD will purchase the first doses of the COVID-19 antibody as part of Operation Warp Speed's goals to deliver coronavirus treatments to patients by the end of 2020. PHARMANEWS INTELLIGENCE https://pharmanewsintel.com/news/eli-lilly-strikes-deal-with-govt-over-covid-19-antibody-drug

643) 2020-10-30 Regeneron: REGN-COV2 independent data monitoring committee recommends holding enrollment in hospitalized patients with high oxygen requirements and continuing enrollment in patients with low or no oxygen requirements. https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends ***Please note, this announcement confirms that antibody therapy should be administered early (<72 hours) in the clinical course of all individual COVID-19 positive patients.***

644) 2020-10-30 McGrail S: Eli Lilly strikes deal with Govt over COVID-19 antibody drug. PHARMANEWS INTELLIGENCE xtelligent HEALTHCARE MEDIA. https://pharmanewsintel.com/news/eli-lilly-strikes-deal-with-govt-over-covid-19-antibody-drug

645) 2020-11 Simoneaux R, Shafer SL: A RAS and Bradykinin-mediated mechanism for COVID-19. ASA Monitor 2020 November; 84: 1-11. https://pubs.asahq.org/monitor/article/84/11/1/110833/A-RAS-and-Bradykinin-Mediated-Mechanism-for-COVID

646) 2020-11 Liu STH, Lin HM, Biane I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A Bander J, Sanky C, Dupper A, Zheng A, Nguyen FT, Amanat F, Stadlbauer D, Altman DR, Chen BK, Krammer F, Mendu DR, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM: Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nature Medicine 2020 November; 26: 1708-1713. https://www.nature.com/articles/s41591-020-1088-9

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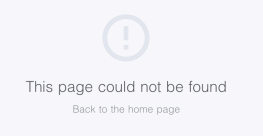
…This retrospective, propensity score-matched case-control study assessed the effectiveness of convalescent plasma therapy in 39 patients with severe or life-threatening COVID-19 at the Mount Sinai Hospital in New York City. Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of propensity score-matched controls who were hospitalized with COVID-19 (adjusted odds ratio (OR), 0.86; 95% confidence interval (CI), 0.75-0.98; chi-square test P value=0.025. Survival also improved in plasma receipients (adjusted hazard ratio (HR), 0.34; 95% CI, 0.13-0.89; chi-square test P value=0.027). Convalescent plasma is potentially effective against COVID-19, but adequately powered, randomized controlled trials are needed.

647) 2020-11-01 Echevarria K: Remdesivir (VEKLURY) Criteria for use November 2020. U.S. Department of Veterans Affairs, Veteran Health Administration, VA Pharmacy Benefits Management Services 10P4P. https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf

In my preparation of my dutiful submission in January 2022, when I attempted to access the URL above on January 5, 2022, the following came up:



When one clicks on: "Back to the home page" https://vanf.app/ :

This is flagrant electronic destruction of official U.S. government documentation by a Service of an Agency of the Executive Branch of the U.S. Federal Government: VA Pharmacy Benefits Management Services 10PAP, Veterans Health Administration, U.S. Department of Veterans Affairs, which is overseen by Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliated Networks (DEAN). Below is the document that has been removed from the Internet that contains erroneous information in the "**Inclusion Criteria**."

When one clicks on: "Back to the home page" https://vanf.app/ :

This is flagrant electronic destruction of official U.S. government documentation by a Service of an Agency of the Executive Branch of the U.S. Federal Government: VA Pharmacy Benefits Management Services 10PAP, Veterans Health Administration, U.S. Department of Veterans Affairs, which is overseen by Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliated Networks (DEAN).

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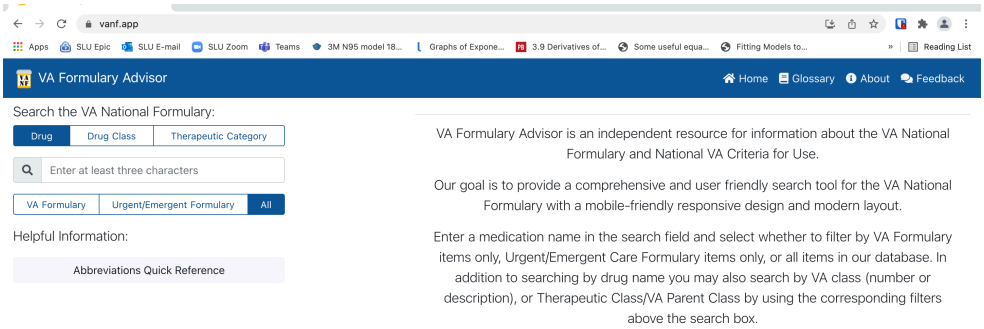
Below is the document that has been removed by the VA from the Internet that contains erroneous information in the "**Inclusion Criteria**." THE DOCUMENT BELOW FROM THE VA Pharmacy Benefits Management Services remained under the URL above for several months! Even using the Wayback Machine, ***Remdesivir (VEKLURY) Criteria for Use November 2020*** cannot be found today! --Charles Andrus, M.D., F.A.C.S. 5/14/2022


vanf.app
VA Formulary Advisor
Home
Glossary
About
Feedback
Search the VA National Formulary:
Drug
Drug Class
Therapeutic Category
Enter at least three characters
VA Formulary
Urgent/Emergent Formulary
All
Helpful Information:
Abbreviations Quick Reference
VA Formulary Advisor is an independent resource for information about the VA National Formulary and National VA Criteria for Use.
Our goal is to provide a comprehensive and user friendly search tool for the VA National Formulary with a mobile-friendly responsive design and modern layout.
Enter a medication name in the search field and select whether to filter by VA Formulary items only, Urgent/Emergent Care Formulary items only, or all items in our database. In addition to searching by drug name you may also search by VA class (number or description), or Therapeutic Class/VA Parent Class by using the corresponding filters above the search box.

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY)
Criteria for Use
November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at *www.pbm.va.gov* or *http://vaww.pbm.va.gov* for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive remdesivir

- ☐ Treated for COVID-19 as an outpatient
- ☐ AST or ALT > 5 times the upper limit of normal
- ☐ Hospitalized patients but NOT requiring supplemental oxygen*
- ☐ Concomitant use of hydroxychloroquine or chloroquine
- ☐ Current eGFR < 30 mL/min**

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

- ☐ Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

Supplemental Information

Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given

**Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis*

***Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.*

****Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19*

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

Updated version may be found at *PBM INTERnet* or *PBM INTRAnet*

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

648) 2020-11-03 Epstein J, Smid WM, Wendel S, Somuah D, Burnouf T: Plasma-Based COVID-19 treatments in low-and middle- income countries and the risk of transfusion-transmitted infections. Npj | Vaccines, www.nature.com/npjvaccines https://www.nature.com/articles/s41541-020-00256-6.pdf From 1995 to 2017, Dr. Epstein was the Director, Office of Blood Research and Review, CBER, FDA. https://www.who.int/biologicals/expert_committee/BIO_EPSTEIN_Jay_2018.pdf

649) 2020-11-05 Aljazeera: Regeneron hopes US will greenlight COVID-19 antibody durg soon. https://www.aljazeera.com/economy/2020/11/5/regeneron-hopes-us-will-green-light-covid-19-antibody-drug-soon

> Regeron Pharmaceuticals Inc said United States health regulators were doing a careful analysis of its experimental antibody cocktail to treat COVID-19 and that it was hopeful the drug could be authorized for emergency use in the country soon. …
>
> …Based on clinical trials, Regeneron expects emergency use authorisation could be granted for outpatients, a group that it believes would benefit the most from the drug.
>
> About 80,000 doses of the treatment could be ready by the end of this month, and 300,000 doses by the end of January, Regeneron said.

650) 2020-11-05 Beigel JH, Tomasek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Oh M, Ruiz-Palacios GM, Benfield T, Fatkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, and Lane HC for the ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 – Final Report. N Engl J Med 2020 Nov 5; 383 (19); 1813-1826. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764?articleTools=true

> (ABSTRACT) CONCLUSIONS Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.) **PLEASE NOTE THAT THIS STUDY WAS FUNDED "PRIMARILY" BY THE NIAID OF WHICH Dr. Fauci is the Director.** FROM NOVEMBER 5, 2020, TO THE PRESENT EVERY MAN, WOMAN, AND CHILD WHO CONTRACTED COVID-19 SHOULD HAVE BEEN OFFERED REMDESIVIR AS SOON AS THEY TESTED POSITIVE.
>
> Page 1814: …Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase with in vitro inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV),5-8 was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit SARS-CoV-2 in vitro.9 In addition, in nonhuman primate studies,

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remdesivir initiated 12 hours after inoculation with MERS-CoV10,11 reduced lung virus levels and lung damage.

To evaluate the clinical efficacy and safety of putative investigational therapeutic agents among hospitalized adults with laboratory-confirmed Covid-19, we designed an adaptive platform trial to rapidly conduct a series of phase 3, randomized, double-blind, placebo-controlled trials. Here, we describe the first stage of the Adaptive Covid-19 Treatment Trial (ACTT-1), in which we evaluated treatment with remdesivir as compared with placebo. The results presented here represent an update to a preliminary report after complete follow-up.

Page 1825: …Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratoryconfirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients.

Page 1825: …**The trial was sponsored and primarily funded by the NIAID, National Institutes of Health (NIH), Bethesda, MD. This trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, under contract HHSN261200800001E 75N910D00024, task order number 75N91019F00130/75N91020F00010, and by the Department of Defense, Defense Health Program. This trial has been supported in part by the NIAID of the NIH under award numbers UM1AI148684, UM1AI148576, UM1AI148573, UM1AI148575, UM1AI148452, UM1AI148685, UM1AI148450, and UM1AI148689.** The trial has also been funded in part by the governments of Denmark, Japan, Mexico, and Singapore. The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council (MRC _UU_12023/23).

651) 2020-11-06 Lupkin S: Federal supply deal for COVID-19 antibody treatment lacks some customary protections. NPR. https://www.npr.org/sections/health-shots/2020/11/06/931795256/federal-supply-deal-for-covid-19-antibody-treatment-lacks-some-customary-protect

652) 2020-11-08 Tenny S, Varacallo M: Evidence Based Medicine. Treasure Island, FL: StatPearls Publishing, 2o21 Jan https://www.ncbi.nlm.nih.gov/books/NBK470182/

653) 2020-11-09 Hinton DM: Emergency Use Authorization regarding Eli Lilly's bamlanivimab. U.S. Food & drug, November 10, 2021. http://web.archive.org/web/20201109232745/https://www.fda.gov/media/143602/download

654) 2020-11-09 Food and Drug Administration: Coronavirus (COVID-19) update: FDA authorizes monoclonal antibody for treatment of COVID-19. FDA news release, November 9, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19

655) 2020-11-09 Centers for Medicare and Medicaid: Medicare monoclonal antibody COVID-19 infusion program instruction. First issued about November 12, 2020 but is not dated so this is the present version in May 2021.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

https://www.cms.gov/files/document/covid-medicare-monoclonal-antibody-infusion-program-instruction.pdf The present version gives the history of these instructions and provides for any physician to be able administer these to patients under the EUAs:

> On November 9, 2020, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy, bamlanivimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients with positive COVID-19 test results who are at high risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. Review the Fact Sheet for Health Care Providers EUAof Bamlanivimabregarding the limitations of authorized use.
>
> On November 21, 2020, the FDA issued an EUA for the investigational monoclonal antibody therapy, casirivimab and imdevimab, administered together, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients with positive COVID-19 test results who are at high risk for progressing to severe COVID-19 and/or hospitalization. As with the other monoclonal antibody infusion treatments, casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.Review the Fact Sheet for Health Care Providers EUAof Casirivimab and Imdevimab regarding the limitations of authorized use when administered together.
>
> On February 9, 2021, the FDA issued an EUAfor the investigational monoclonal antibody therapy, bamlanivimab and etesevimab, administered together, for the treatment of mild-to-moderate COVID19 in adults and pediatric patients with positive COVID-19 test results who are at high risk for progressing to severe COVID-19 and/or hospitalization. As with the other monoclonal antibody infusion treatments, bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.Review the Fact Sheet for Health Care Providers EUA of Bamlanivimab and Etesevimab regarding the limitations of authorized use when administered together.
>
> During the COVID-19 public health emergency (PHE), Medicare will cover and pay for these infusions (when furnished consistent with their respective EUAs) the same way it covers and pays for COVID-19 vaccines.
>
> This would allow a broad range of providers and suppliers, including freestanding and hospital-based infusion centers, home health agencies, nursing homes, and entities with whom nursing homes contract for this, to administer these treatments in accordance with the EUA. Medicare will not pay for the COVID-19 monoclonal antibody products that providers receive for free. If providers begin to purchase COVID-19 monoclonal antibody products, Medicare anticipates setting the payment rate for the products, which will be 95% of the average wholesale price (AWP) for many health care providers, consistent with usual vaccine payment methodologies. Additionally, Medicare anticipates establishing codes and rates for the administration of the products.
>
> In order to facilitate the efficient administration of COVID-19 vaccines to SNF residents, CMS will exercise enforcement discretion with respect to certain statutory provisions as well as any associated statutory references and implementing regulations, including as interpreted in pertinent guidance (collectively, "SNF Consolidated Billing Provisions"). Through the exercise of that discretion, CMS will allow Medicare-enrolled immunizers including, but not limited to,

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

pharmacies working with the United States, as well as infusion centers, and home health agencies to bill directly and receive direct reimbursement from the Medicare program for vaccinating Medicare SNF residents.

Health care providers administering the COVID-19 monoclonal antibody infusions will follow the same enrollment process as those administering the other COVID-19 vaccines. Review provider enrollment information. https://www.cms.gov/medicare/covid-19/enrollment-administering-covid-19-vaccines

656) 2020-11-09 Lilly INVESTORS: Lilly's neutralizing antibody bamlanivimab (LY-CoV555) receives FDA emergency use authorization for the treatment of recently diagnosed COVID-19. https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-receives-fda

657) 2020-11-09 Lee SM: The FDA has authorized the COVID-19 antibody drug that Christie took—Eli Lilly's experimental coronavirus therapy, bamlanivimab, received an emergency use authorization for mild to moderate COVID-19. BuzzFeed News https://www.buzzfeednews.com/article/stephaniemlee/fda-coronavirus-antibody-therapy-eli-lilly

658) 2020-11-10 Hinton DM: Emergency Use Authorization regarding Eli Lilly's bamlanivimab. U.S. Food & drug, November 10, 2021. http://web.archive.org/web/20210123043558/https://www.fda.gov/media/143602/download

659) 2020-11-10 Centers for Medicare and Medicaid: CMS takes steps to ensure medicare beneficiaries have wide access to COVID-19 antibody treatment. https://www.cms.gov/newsroom/press-releases/cms-takes-steps-ensure-medicare-beneficiaries-have-wide-access-covid-19-antibody-treatment This is printed *verbatim*:

Updated: November 13, 2020

The Centers for Medicare & Medicaid Services announced that starting today, Medicare beneficiaries can receive coverage of monoclonal antibodies to treat coronavirus disease 2019 (COVID-19) with no cost-sharing during the public health emergency (PHE). CMS' coverage of monoclonal antibody infusions applies to bamlanivimab, which received an emergency use authorization (EUA) from the U.S. Food and Drug Administration yesterday.

"Today, CMS is announcing a historic, first-of-its kind policy that drastically expands access to COVID-19 monoclonal antibodies to beneficiaries without cost sharing," said CMS Administrator Seema Verma. "Our timely approach means beneficiaries can receive these potentially life-saving therapies in a range of settings – such as in a doctor's office, nursing home, infusion centers, as long as safety precautions can be met. This aggressive action and innovative approach will undoubtedly save lives."

CMS anticipates that this monoclonal antibody product will initially be given to health care providers at no charge. Medicare will not pay for the monoclonal antibody products that providers receive for free but today's action provides for reimbursement for the infusion of the

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Prevention: *Active Immunization*: Vaccines

product. When health care providers begin to purchase monoclonal antibody products, Medicare anticipates setting the payment rate in the same way it set the payment rates for COVID-19 vaccines, such as based on 95% of the average wholesale price for COVID-19 vaccines in many provider settings. This means that cases that include the use of monoclonal antibody COVID-19 products will not be eligible for the enhanced payment established under the Medicare Inpatient Prospective Payment System (IPPS) in CMS-9912-IFC. CMS will issue billing and coding instructions for health care providers in the coming days.

CMS anticipates the announcement today will allow for a broad range of providers and suppliers, including freestanding and hospital-based infusion centers, home health agencies, nursing homes, and entities with whom nursing homes contract, to administer this treatment in accordance with the EUA, and bill Medicare to administer these infusions.

Under section 6008 of the Families First Coronavirus Response Act (FFCRA), state and territorial Medicaid programs may receive a temporary 6.2 percentage point increase in the Federal Medical Assistance Percentage (FMAP), through the end of the quarter in which the COVID-19 PHE ends. A condition for receipt of this enhanced federal match is that a state or territory must cover COVID-19 testing services and treatments, including vaccines and their administration, specialized equipment, and therapies for Medicaid enrollees without cost sharing. This means that this monoclonal antibody infusion is expected to be covered when furnished to Medicaid beneficiaries, in accordance with the EUA, during this period, with limited exceptions.

To view the Monoclonal Antibody COVID-19 Infusion Program Instruction, visit: https://www.cms.gov/files/document/covid-medicare-monoclonal-antibody-infusion-program-instruction.pdf

660) 2020-11-10 Skovronsky D: When the World called for help with COVID-19, We were ready. https://www.lilly.com/news/stories/daniel-skovronsky-covid19-scientific-discovery-innovation

661) 2020-11-10 HHS.gov: HHS allocates Lilly therapeutic to treat patients with mild to moderate COVID-19. https://www.hhs.gov/about/news/2020/11/10/hhs-allocates-lilly-therapeutic-treat-patients-mild-moderate-covid-19.html

662) 2020-11-11 Anwar MM, Badawi AM, Eltablawy NA: Can the coronavirus infection penetrates the brain resulting in sudden anosmia followed by severe neurological disorders? https://reader.elsevier.com/reader/sd/pii/S2405650220300691?token=2704FCAE9A6F6D340EB856A4E818BA899B840BC12513B2D39B8685B9A829472E4EB406237115DC34E3E457E8AA668EBF&originRegion=us-east-1&originCreation=20220321010145

https://ars.els-cdn.com/content/image/1-s2.0-S2405650220300691-gr1_lrg.jpg

663) 2020-11-11 Sidarta-Oliveira D, Jara CP, Ferruzzi AJ, Skaf MS, Velander WH, Araujo EP, Velloso: SARS-CoV-2 receptor is co-expressed with elements of the kinin-kallikrein, renin-angiotensin and coagulation systems in alveolar cells. *Nature* Scientific Reports 11 November 2020; 10, article number 19522 (2020)b https://www.nature.com/articles/s41598-020-76488-2

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664) 2020-11-12 Farr C: Bioethicists worry the rich and powerful will get special access to experimental Covid treatments. www.cnbc.com https://www.cnbc.com/2020/11/12/coronavirus-bioethicists-worry-the-rich-and-powerful-will-get-special-access-to-experimental-treatments-.html

665) 2020-11-13 Thomas K, Weiland N: Eli Lilly's antibody treatment gets Emergency F.D.A. Approval. The New York Times. https://www.nytimes.com/2020/11/10/world/the-fda-grants-emergency-authorization-of-eli-lillys-antibody-treatment.html

666) 2020-11-16 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. November 16, 2020. https://web.archive.org/web/20210114142146/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

667) 2020-11-16 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry. https://web.archive.org/web/20201117201040/https://www.fda.gov/media/136798/download

668) 2020-11-17 O'Donnell C, Threlfall A: Regeneron says Roche successfully tested manufacture of COVID-19 drug used on Trump. Reuters. https://www.reuters.com/article/us-health-coronavirus-regeneron/regeneron-says-roche-successfully-tested-manufacture-of-covid-19-drug-used-on-trump-idUSKBN27X2T5

669) 2020-11-18 Andrus CH: 1 Dear Mr President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. U.S. Copyright Office, 2020-11-18, TXu002232947. https://web.archive.org/web/20210904021628/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=3&ti=1%2C3&Search_Arg=andrus+charles+h&Search_Code=NALL&CNT=25&PID=py6zcjaddPxEbahiUXXmsV0vRNwjXMy&SEQ=20210512081735&SID=2

670) 2020-11-20 CNBC Squawk Box: Former FDA chief Gottlieb says remdesivir still provides treatment benefit for hospitalized Covid-19 patients. https://www.cnbc.com/video/2020/11/20/former-fda-chief-gottlieb-says-remdesivir-still-provides-treatment-benefit-for-hospitalized-covid-19-patients.html

671) 2020-11-21 Langreth R, LaVito A: Regeneron gets emergency U.S. clearance for Covid-19 therapy. Bloomberg. https://www.bloomberg.com/news/articles/2020-11-22/regeneron-gets-emergency-u-s-clearance-for-covid-19-therapy

672) 2020-11-21 Hinton DM: U.S. Food & Drug Administration Letter to Regeneron Emergency Use Authorization (EUA) regarding casirivirimab and imdevimab cocktail. November 21, 2021. https://www.fda.gov/media/143891/download

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673) 2020-11-21 Food and Drug Administration: Coronavirus (COVID-19) update: FDA authorizes monoclonal antibody for treatment of COVID-19. FDA news release, November 21, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19

674) 2020-11-22 Fauci A: Transcript: Anthony Fauci on "Face the Nation," November 22, 2020. https://www.cbsnews.com/news/transcript-anthony-fauci-on-face-the-nation-november-22-2020/

675) 2020-11-22 U.S. Food & Drug Administration: Fact sheet for health care providers emergency use authorization (EUA) of Casirivimab and Imdevimab. http://web.archive.org/web/20201122011932/https://www.fda.gov/media/143892/download *Please note that this fact sheet regarding Regeneron's monoclonal antibody cocktail exists to this day.* ***The criteria for administration of casirivimab and imdevimab in the Black Box is stated for only in patients who have mild to moderate symptoms outside of hospital "…at high risk for progressing to severe COVID-19 and/or hospitalization…" This is arbitrarily based on a physician's ability to predict the future outcome of the individual patient regarding administration to or withholding from early in the disease process of the individual patient and has led to withholding of casirivimab and imdevimab and thus de facto rationing of a safe treatment that should be available to all people who become COVID-19 positive within 72 hours of positivity.***

676) 2020-11-21 Regeneron: Regeneron's casirivimab and imdevimab antibody cocktail for COVID-19 is first combination therapy to receive FDA Emergency Use Authorization. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regen-cov2-first-antibody-cocktail-covid-19-receive

677) 2020-11-23 Higgins-Dunn N: Regeneron will provide 300,000 doses of Covid treatment for U.S. by early January, CEO Schleifer says. CNBC Health and Science, published Mon, Nov 23, 2020, 10:20 AM EST, updated Mon, Nov 23, 2020, 11:14 AM EST. https://www.cnbc.com/2020/11/23/regeneron-will-provide-300000-doses-of-covid-treatment-for-us-by-early-january-ceo-schleifer-says.html#:~:text=Squawk%20Box-,Regeneron%20will%20provide%20the%20U.S.%20with%20300%2C000%20doses%20of%20its,treatment%2C%20called%20REGN%2DCOV2.

> Regeneron will provide the U.S. with 300,000 doses of its newly authorized Covid-19 antibody treatment by early January, the company's CEO, Dr. Leonard Schleifer, said Monday.
>
> The Food and Drug Administration on Saturday granted an emergency use authorization for the company's antibody treatment, called REGN-COV2. The experimental therapy was given to President Donald Trump when he contracted the coronavirus in October.

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In July, the federal government, as part of the Trump administration's Operation Warp Speed, gave Regeneron $450 million in funding to support manufacturing of the drug.

Schleifer told CNBC's "Squawk Box" on Monday that the company has 80,000 doses of its antibody treatment immediately ready for distribution. The federal government will be responsible for allocating the doses to the states "proportion to the need and amount of Covid," he said.

After January, Regeneron will have the ability to supply 100,000 doses every month, Schleifer said. The company is also conducting experiments to determine whether the dosage can be cut in half, which would eventually double the amount of available doses to 200,000 every month if proven effective, he said.

678) 2020-11-23 Samad N, Sodunke TE, Banna HA, Sapkota A, Fatema AN, Iskandar K, Jahan D, Hardcastle TC, Nusrat T, Chowdhury TS, Haque M: Convalescent plasma therapy for management of COVID-19: Perspectives and deployment in the current global pandemic. Dovepress. https://www.dovepress.com/convalescent-plasma-therapy-for-management-of-covid-19-perspectives-an-peer-reviewed-fulltext-article-RMHP

Extensive review of the world literature outlining both the pros, cons, and mixed outcomes in the utilization of Convalescent Plasma.

679) 2020-11-24 Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, Savoy N, Giunta, Perez LG, Sanchez M.L., Gamarnik AV, Ojeda DS, Santoro DM, Camino PJ, Antelo S, Raineo K, Vidiella GO, Miyazaki EA, Cornistein W, Trabadelo OA, Spotti M, Funtowicz G, Scordo WE, Losso MH, Ferniot I, Pardo PE, Rodriguez E, Rucci P, Pasquali J, Fuentes NA, Esperatti M, Speroni GA, Nannini EC, Matteaccio A, Michelangelo HG, Follmann D, Lane HC, Belloso W, for the PlasmAr Study Group*: A randomized trial of convalescent plasma in Covid-19 Severe Pneumonia, PlasmAR ClinicalTrials.gov number, NCT04383535. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2031304, November 24, 2020, 1-11. Republished by N Engl J Med, February 18, 2021; 384 (7): 619 – 629. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031304?articleTools=true

680) 2020-11-25 Majra D, Benson J, Pitts J, Stebbing J: Review: SARS-CoV-2 (COVID-19) superspreader events. Journal of Infection 2021; 82: 36-40. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685932/pdf/main.pdf

681) 2020-11-25: van Beusekom: M: Studies find no COVID benefit for preventive hydroxychloroquine or for convalescent plasma. CIDRAP, Center for Infectious Disease Research and Policy, University of Minnesota. https://www.cidrap.umn.edu/news-perspective/2020/11/studies-find-no-covid-benefit-preventive-hydroxychloroquine-or-convalescent

No differences in clinical status, outcomes
In the second study, a double-blind, randomized trial, a research team led by scientists with Hospital Italiano de Buenos Aires in Argentina compared the outcomes of 228 hospitalized

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COVID-19 patients with severe pneumonia and low oxygen levels at 12 sites who received 500 milliliters of convalescent plasma with those of 105 patients who received a placebo.

682) 2020-11-26 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. November 16, 2020. https://web.archive.org/web/20210114142146/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

683) 2020-11-30 Russell MW, Moldoveanu Z, Ogra PL, Mestcecky J: Mucosal Immunity in COVID-19: A neglected but critical aspect of SARS-CoV-2 infection. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7733922/pdf/fimmu-11-611337.pdf

684) 2020-11-30 Hinton DM: U.S. Food & Drug Administration Emergency Utilization Authorization (EUA) Letter to Robert P. Kadlec, MD, MTM&H, MS, Assistant Secretary for Preparedness and Response, issuing the EUA on COVID-19 Convalescent Plasma. U.S. Food & Drug, November 30, 2020. https://web.archive.org/web/20210106221857/https://www.fda.gov/media/141477/download

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686) 2020-12-04 Rezaie S: BLAZE-1 COVID-19 neutralizing antibody (Bamlanivimab). REBE EM – Emergency Medicine Blog. https://rebelem.com/blaze-1-covid-19-neutralizing-antibody-bamlanivimab/

687) 2020-12-07 McGrail S: US Govt purchases additional 650,000 doses of COVID-19 antibody. PHARMANEWS INTELLIGENCE xtelligent HEALTHCARE MEDIA. https://pharmanewsintel.com/news/us-govt-purchases-additional-650000-doses-of-covid-19-antibody

688) 2020-12-08 Schoenfeld-Walker A, Conlen M: Tracking coronavirus infections in The White House and Trump's Inner Circle. The New York Times, original 11/11/2020 and updated 12/8/2020. https://www.nytimes.com/interactive/2020/11/11/us/politics/white-house-covid-outbreak.html

689) 2020-12-09 Stolberg SG: Trump and friends got coronavirus care many others couldn't. Rudolph W. Giuliani became the latest in President Trump's inner circle to boast about the treatment he received for Covid-19, as hospitals across the country ration care. The New York Times. https://web.archive.org/web/20201210042553/https://www.nytimes.com/2020/12/09/us/politics/trump-coronavirus-treatments.html

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WASHINGTON — Ben Carson, Chris Christie and Donald J. Trump are not the sturdiest candidates to conquer the coronavirus: older, in some cases overweight, male and not particularly fit. Yet all seem to have gotten through Covid-19, and all have gotten an antibody treatment in such short supply that some hospitals and states are doling it out by lottery.

Now Rudolph W. Giuliani, the latest member of President Trump's inner circle to contract Covid-19, has acknowledged that he received at least two of the same drugs the president received. He even conceded that his "celebrity" status had given him access to care that others did not have.

"If it wasn't me, I wouldn't have been put in a hospital frankly," Mr. Giuliani, the president's personal lawyer, told WABC radio in New York. "Sometimes when you're a celebrity, they're worried if something happens to you they're going to examine it more carefully, and do everything right."

Mr. Giuliani's candid admission once again exposes that Covid-19 has become a disease of the haves and the have-nots. The treatment given to Mr. Trump's allies is raising alarms among medical ethicists as state officials and health system administrators grapple with gut-wrenching decisions about which patients get antibodies in a system that can only be described as rationing.

"We should not have Chris Christie and Ben Carson — and in the case of Carson with intervention by the president — get access," said Arthur Caplan, a medical ethicist who works with drug companies on how to ration scarce medicines, referring to the secretary of housing and urban development's admission that the president "cleared" him for the therapy. "That is not the way to secure public support for difficult rationing systems."

The treatments — a monoclonal antibody developed by Eli Lilly and a cocktail of two monoclonal antibodies developed by Regeneron — won emergency use authorization, or an E.U.A., from the Food and Drug Administration last month for outpatients with "mild to moderate" disease who are at high risk for progressing to severe disease or for being hospitalized.

With cases soaring, the pool of potential patients is vast.

"One of the challenges is the E.U.A. criteria really are so broad, it could be half of the people with Covid could qualify, but there is clearly not enough," said Erin Fox, the senior pharmacy director for University of Utah Health, who has helped her state draft criteria to determine who is eligible for the drugs. "Unfortunately, that leaves each hospital or each state to develop their own rationing criteria."

Even some top officials at the F.D.A. — both career employees and political appointees — have privately expressed concern in recent months that people with connections to the White House appeared to be getting access to the antibody treatments, according to three senior administration officials.

Mr. Giuliani, 76, appeared unaware of the scarcity issues, telling interviewers that politicians have taken masks and business closures too far now that Covid-19 is "a treatable disease."

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

In fact, the antibody treatments are so scarce that officials in Utah have developed a ranking system to determine who is most likely to benefit from the drugs, while Colorado is using a lottery system. Dr. Matthew Wynia, director of the Center of Bioethics and Humanities at the University of Colorado, said that giving the powerful access was patently unfair.

"That's one of the reasons why we decided that we would allocate this only through the state and only through this random allocation process," he said, "so that no one could get a leg up by virtue of their special connections."

And there are other complicating factors keeping many people from getting the therapies as well. The infusions must be administered in outpatient settings, but infusion centers, which also care for immune-suppressed cancer patients, are loath to treat people who have an infectious disease. And many emergency rooms are so overrun that they do not have the space.

In Utah, Dr. Fox said her hospital had shipped much of the supply of antibodies to rural hospitals, which had more room. Both she and Dr. Wynia in Colorado expressed concern that the therapies might not be distributed equitably across racial and ethnic lines, with hard-hit minority communities not getting their fair share.

The scarcity is such a problem that the National Academies of Sciences, Engineering and Medicine is holding a session next week to help medical professionals sort their way through rationing questions.

"We've been trying to get the word out so that as patients might get a positive test they could get information that they might qualify for treatment, but that only works for people with a lot of resources," Dr. Fox said.

Politicians are not the only ones with resources getting access.

In an interview on Wednesday, one prominent businessman, who spoke on condition of anonymity to avoid harming his reputation, described his aggressive efforts to track down the Regeneron treatment — including calling friends who were hospital executives and hospital donors — after he tested positive last week.

Eventually he was directed to an emergency room in his city, which was expecting him. He was given an infusion of the drug on Monday. He is feeling much better, he said.

Both Mr. Trump and Mr. Christie, a longtime friend of his and former New Jersey governor, got the antibodies before they were approved by the F.D.A. Dr. Caplan, the medical ethicist, said he had no problem with Mr. Trump, 74, getting the therapy — he is, after all, the president, "a special person unto him- or herself."

But Mr. Christie's access appeared to be extraordinary. Mr. Christie, 58, was offered participation in a Regeneron clinical trial but turned it down, a person familiar with his treatment said, fearing he might receive a placebo. Instead, he received the Eli Lilly treatment. He is overweight and has asthma, and thus may have been a good candidate,

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Dr. Caplan said, though he wondered if similarly situated patients would have gotten the drug.

Dr. Carson, 69, got the Regeneron cocktail after it was approved, then took to Facebook last month to say he was "desperately ill" with the coronavirus until the president intervened.

"President Trump was following my condition and cleared me for the monoclonal antibody therapy that he had previously received, which I am convinced saved my life," he wrote, adding that "we must prioritize getting comparable treatments and care to everyone as soon as possible."

Mr. Giuliani's treatment is less clear. Calling into ABC Radio from his hospital bed on Tuesday, he said specifically that he had received two drugs — remdesivir, which has F.D.A. approval for treatment of Covid-19, and dexamethasone, a steroid.

But he also said he had received the same treatment "cocktail" as the president: "Exactly the same, his doctor sent me here; he talked me into it," Mr. Giuliani said of Mr. Trump's physician, adding, "The minute I took the cocktail yesterday, I felt 100 percent better. It works very quickly, wow."

The therapies are being allocated by the Department of Health and Human Services to states and jurisdictions based, the department's website says, on a "percentage of the country's total number of confirmed Covid-19 patients and the total number of confirmed hospitalized patients during a seven-day reporting period."

California, for example, has been allocated 17,760 doses of the Eli Lilly therapy and 5,728 doses of the Regeneron cocktail (the Eli Lilly drug is in greater supply). Maine, with many fewer people and Covid-19 cases, has been allocated 330 and 98 doses of those therapies.

Health Secretary Alex M. Azar II told reporters on Wednesday that so far, 278,000 doses of the two therapies have been allocated. There were almost that many coronavirus cases (220,225) diagnosed in the United States on Tuesday alone.

Once state and local health agencies determine which hospitals or medical facilities should get the drugs, they are shipped out by a third-party distributor. Then it is up to health care providers to figure out what to do with them. Dr. Peter L. Slavin, the president of Massachusetts General Hospital, said in an interview Tuesday that access there would be by lottery.

"The notion that we are going to be able to treat a significant percentage of the people who qualify for the drug with the drug — it's not going to happen," he said.

Noah Weiland and Katie Thomas contributed reporting.

690) 2020-12-10 Goldberg M: Covid meds are scarce but not for Trump cronies – Rudy Giuliani got monoclonal antibodies. You probably can't. The New York Times. https://web.archive.org/web/20201211074255/https://www.nytimes.com/2020/12/10/opinion/coronavirus-giuliani-regeneron.html

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Prevention: *Active Immunization*: Vaccines

691) 2020-12-13 Andrus CH: Letter to the Editor of the New England Journal of Medicine regarding treatment with and synergy of ***Passive Immunization*** regarding the SARS-CoV-2 virus infection. ***The editors of NEJM ignored the letter but on January 6, 2021 published the landmark article (appropriately age stratified and COVID-19 Convalescent Plasma given within 72 hours of diagnosis): Libster, et. al.: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true

692) 2020-12-14 Dixit S: Who is Jeffrey Rosen's wife Kathleen Rosen? A look at acting AG's 37-year marriage, children and love for travel. https://meaww.com/jeffrey-rosen-wife-doctor-kathleen-married-37-years-children-travel

693) 2020-12-16 Manis JP: Overview of therapeutic monoclonal antibodies. UpToDate. https://www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies/print

694) 2020-12-16 Tirrell M: Antibody drugs used to treat Trump, others could cut Covid-19 hospitalizations by half, but they're not being used by the general public. CNBC. https://www.msn.com/en-us/money/markets/antibody-drugs-used-to-treat-trump-others-could-cut-covid-19-hospitalizations-by-half-but-they-re-not-being-used-by-the-general-public/ar-BB1bZaPX?li=BBnba9O

695) 2020-12-16 Hinton DM: BinaxNOW COVID-19 Ag Card. Abbott Diagnostics Scaborough, Inc. https://www.fda.gov/media/141567/download and with regards to sensitivity and specificity: Pollreis RE, *et al*: Evaluation of the Abbott BinaxNOW COVID-19 Test Ag Card for rapid detection of SARS-CoV-2 infection by a local public health district with a rural population. PLOS ONE. 2021-12-02. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8638850/pdf/pone.0260862.pdf

696) 2020-12-17 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J, Perry C, Pan C, Hosain R, Mahmood A, Davis JD, Turner KC, Hooper AT, Hamilton JD, Baum A, Kyratsous CA, Kim Y, Cook A, Kampman W, Kohli A, Sachdeva Y, Graber X, Kowal B, DiCioccio T, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, for the Trial Investigators. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. December 17, 2021 NEJM.org, N Engl J Med 2021; 384:238-251. https://www.nejm.org/doi/pdf/10.1056/NEJMe2034495?articleTools=true

697) 2020-12-20 Andrus CH: E-mail submitted to Dr. Richard Stone, M.D., Chief Medical Executive (acting Under Secretary of the Veterans Health Administration), regarding the WRONG INCLUSION CRITERIA which contradicted the FDA directive of early administration in the course of COVID-19 disease (<72 hours from diagnosis) going forward from August 28, 2020 **to the present**, regarding Remdesivir (an FDA -approved licensed

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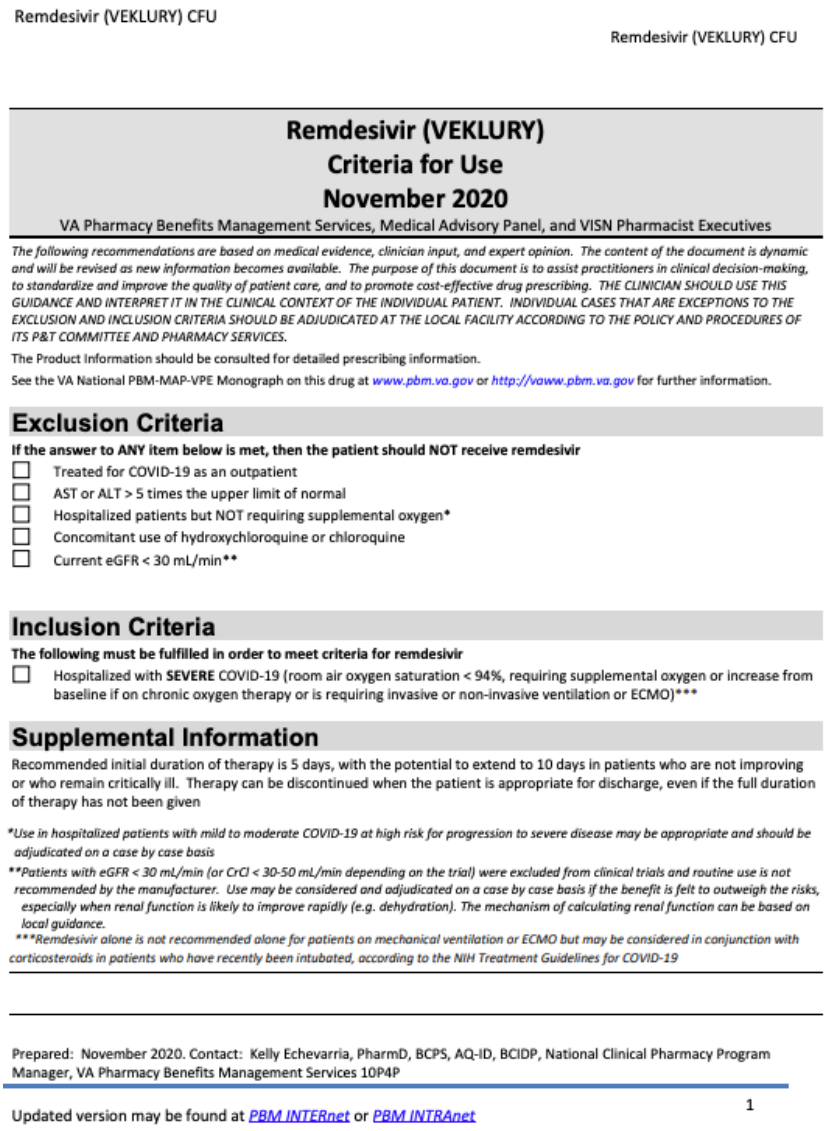
drug: NDA# 214787). This ERRONEOUS DIRECTIVE was still published on the Internet as of October 3, 2021—not having been retracted by the Veterans Health Administration (VHA)—**SHAME ON THE VHA**! The URL is no longer available. https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf What use to be at this U.S. Department of Veterans Affairs website is the following page that directed the administration of Remdesivir at the wrong time.



Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY)
Criteria for Use
November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at *www.pbm.va.gov* or *http://vaww.pbm.va.gov* for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive remdesivir

- ☐ Treated for COVID-19 as an outpatient
- ☐ AST or ALT > 5 times the upper limit of normal
- ☐ Hospitalized patients but NOT requiring supplemental oxygen*
- ☐ Concomitant use of hydroxychloroquine or chloroquine
- ☐ Current eGFR < 30 mL/min**

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

- ☐ Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

Supplemental Information

Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given

**Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis*

***Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.*

****Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19*

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

Updated version may be found at *PBM INTERnet* or *PBM INTRAnet*

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698) 2020-12-22 Pollard AJ, Bijker EM: A guide to vaccinology: from basic principles to new developments. Nature reviews immunology 2021; 21: 83-100. https://www.nature.com/articles/s41577-020-00479-7

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699) 2020-12-23 Thomas K, Robbins R: What to know about the Covid antibody drugs that could help many. The New York Times, Updated Jan 12, 2021. https://web.archive.org/web/20201223152514/https://www.nytimes.com/2020/12/23/health/covid-antibody-treatment.html

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701) 2020-12-24 Goodman KE, Harris AD, Hoffmann DE: Legal challenges to allocating new COVID-19 antibody therapies to those who need them most. Health Affairs Blog. https://www.healthaffairs.org/do/10.1377/hblog20201222.609517/full/

702) 2020-12-28 Sandborg CI, Hartman GE, Su F, Williams G, Teufe, Wixson N, Larson DB, Donnelly: Optimizing professional practice evaluation to enable a nonpunitive learning health system approach to peer review. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7781295/pdf/pqs-6-e375.pdf

703) 2020-12-29 Nickitas P: It shouldn't be this hard to serve your country by David Shulkin. Jewish War Veterans of the United States of America 2020; 74 (4). https://www.jwv.org/it-shouldnt-be-this-hard-to-serve-your-country-by-david-shulkin/

IT SHOULDN'T BE THIS HARD TO SERVE YOUR COUNTRY BY DAVID SHULKIN

By Peter Nickitas, JWV National Judge Advocate

"It Shouldn't Be This Hard to Serve Your Country" describes the public service of the first Jewish-American Secretary of Veterans Affairs, Dr. David Shulkin. Shulkin served as Undersecretary of the VA from 2015 to 2017 and Secretary from 2017 to 2018. Shulkin served as the first chief medical officer of the University of Pennsylvania Health System and CEO of New York's Beth Israel Medical Center before entering public service.

This book makes outstanding reading, as Secretary Shulkin describes his encounters with entrenched officials of the Department of Veterans Affairs (VA) in his work to bring more accountability, veteran-focused care, accessible service, and timely appointments. His accomplishments included updating electronic health records (EHR) systems and expanding Agent Orange treatment to Blue Water Navy veterans who served on ships off the

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Prevention: *Active Immunization*: Vaccines

shore of Vietnam and suffered diseases induced by the Agent Orange clouds that blew offshore. In his words, he found himself with the choice between continued neglect of veterans based on dwindling scientific evidence as veterans died, or the moral choice, and treat Blue Water Navy veterans. He took the moral choice.

He spent a great deal of energy bringing the 2014 Veteran Access, Choice, and Accountability Act up to date in 2017 and 2018, culminating in the Mission Act. At all times, he fought to ensure quality and coordinate the delegation of some care to private providers without eviscerating the core Veterans Affairs budget for VA medical center care. During his time at Secretary, he even saw patients himself at surprise appointments at VA Medical Centers.

Shulkin says his vision for the future of the VA is "a new model of governance, complete with its own board composed of health care experts, veterans, and business leaders. It should remain a government entity but with a structure that allows it to develop strategies free of political influence…. This new governance structure would mean the end of political appointees. People who serve our veterans should be chosen not on the basis of political ideology or their commitment to a particular elected individual but rather because of relevant experience, competence, and commitment to the mission."

"It Shouldn't Be This Hard to Serve Your Country" provides an example of a Jewish-American who as the founders of JWV would say, "redeems the good name of the Jew." Shulkin took the opportunity for service and made the most of it, to show that we Jewish-Americans are capable of fulfilling acts of Torah-Mitzvot and our civic obligations to our nation, our neighbors, and our fellow veterans and servicemembers, with equal fervor and merit.

Volume 74. Number 4. 2020
DECEMBER 29, 2020

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705) 2020-12-31 McGinley L: Only one covid-19 treatment is designed to keep people out of the hospital. Many overburdened hospitals are not offering it. Because of logistical challenges, only 20 percent of monoclonal antibodies distributed by the government have

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been used, officials say. The Washington Post https://www.washingtonpost.com/health/2020/12/31/covid-monoclonal-antibodies-unused/

706) 2021-01-06 Libster R, Pérez Marc, Wappner D, Coviello S, Bianchi A, Braem V, Esteban I, Caballero MT, Wood C, Berruetta M, Rondan A, Lescano G, Cruz P, Ritou Y, Fernández Viña V, Alvarez Paggi D, Esperante S, Ferreti A, Ofman G, Ciganda A, Rodriguez R, Lantos J, Valentini R, Itcovici N, Hintze A, Oyarvide ML, Etcegarary C, Neira A, Name I, Alfonso J, López Castelo R, Caruso G, Rapelius S, Alvez F, Etchenique F, Dimase F, Alvarez D, Aranda SS, Sánchez Yanotti C, De Luca S, Baglivo J, Laudanno S, Nowogrodzki F, Larrea R, Silveyra M, Leberzstein G, Debonis A, Molinos J, González M, Perez E, Kreplak N, Pastor Argüello S, Gibbons L, Althabe F, Bergel E, Polack FP, for the Fundación INFANT-COVID-19 Group*: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true Republished N Engl J Med, February 18, 2021; 384(7): 610 – 618.

707) 2021-01-07 Wray : FBI MOST WANTED – U.S. Capitol Violence. https://www.fbi.gov/wanted/capitol-violence

Director Wray's Statement on Violent Activity at the U.S. Capitol Building

January 7, 2021

The violence and destruction of property at the U.S. Capitol building yesterday showed a blatant and appalling disregard for our institutions of government and the orderly administration of the democratic process. As we've said consistently, we do not tolerate violent agitators and extremists who use the guise of First Amendment-protected activity to incite violence and wreak havoc. Such behavior betrays the values of our democracy. Make no mistake: With our partners, we will hold accountable those who participated in yesterday's siege of the Capitol.

Let me assure the American people the FBI has deployed our full investigative resources and is working closely with our federal, state, and local partners to aggressively pursue those involved in criminal activity during the events of January 6. Our agents and analysts have been hard at work through the night gathering evidence, sharing intelligence, and working with federal prosecutors to bring charges. Members of the public can help by providing tips, information, and videos of illegal activity at fbi.gov/USCapitol. We are determined to find those responsible and ensure justice is served.

708) 2021-01-08 BBC News-Science: What is blood plasma and how does it treat Covid-19? https://www.bbc.com/news/av/science-environment-54665716

709) 2021-01-08 Eli Lilly and Company: 2020 Updates: Lilly's global COVID-19 response. https://www.lilly.com/news/stories/coronavirus-covid19-global-response

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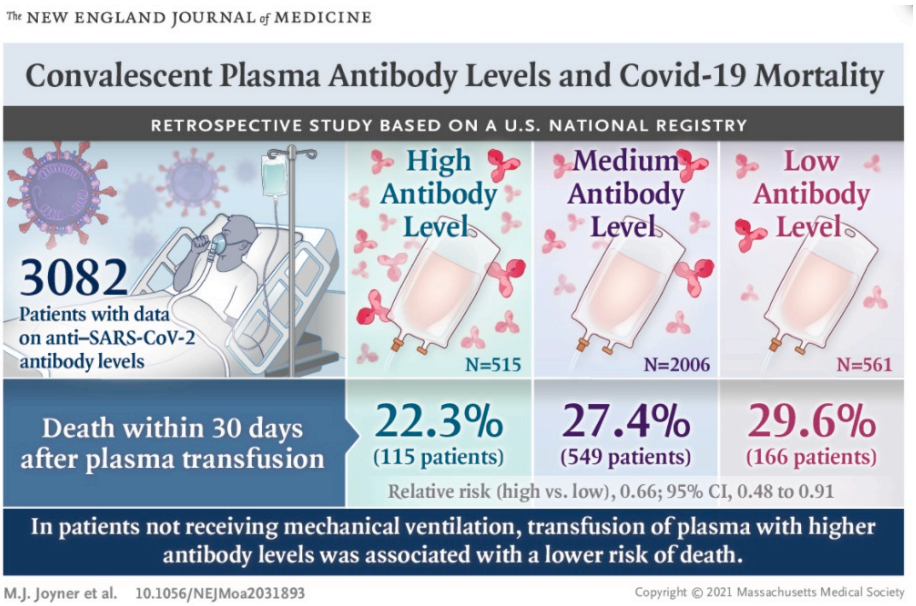
710) 2021-01-08 Hahn S: FDA commissioner Stephen Hahn MD speaks of the coronavirus response. https://www.c-span.org/video/?507805-1/fda-commissioner-dr-stephen-hahn-coronavirus-response

711) 2021-01-12 Regeneron: Regeneron announces U.S. Government agreement to purchase additional COVID-19 antibody cocktail doses. https://investor.regeneron.com/index.php/news-releases/news-release-details/regeneron-announces-us-government-agreement-purchase-additional

712) 2021-01-12 Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Hobartner C, Cramer P: Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nature Communicatioins (2021)12:279 https//doi.org/10.1038/s41467-020-20542-0. https://www.nature.com/articles/s41467-020-20542-0.pdf

713) 2021-01-13 Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea FR, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather D, Wright RS, Casadevall A, *et. al.*: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med, January 13, 2021, at NEJM.org; then republished N Engl J Med 2021; 384:1015-1027. https://www.nejm.org/doi/full/10.1056/NEJMoa2031893


The NEW ENGLAND JOURNAL of MEDICINE
Convalescent Plasma Antibody Levels and Covid-19 Mortality
RETROSPECTIVE STUDY BASED ON A U.S. NATIONAL REGISTRY
3082
Patients with data on anti–SARS-CoV-2 antibody levels
High Antibody Level
N=515
Medium Antibody Level
N=2006
Low Antibody Level
N=561
Death within 30 days after plasma transfusion
22.3% (115 patients)
27.4% (549 patients)
29.6% (166 patients)
Relative risk (high vs. low), 0.66; 95% CI, 0.48 to 0.91
In patients not receiving mechanical ventilation, transfusion of plasma with higher antibody levels was associated with a lower risk of death.
M.J. Joyner et al. 10.1056/NEJMoa2031893
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Conclusions

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> Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.

714) 2021-01-13 McCarthy CG, Wilczynski S,m Wenceslau CF, Webb RC: A new storm on the horizon in COVID-19: Bradykinin-induced vascular complications. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7834250/pdf/main.pdf

715) 2021-01-14 Rodriguez A: US officials urge Americans to ask their doctors about monoclonal antibodies for COVID. But is it too little, to late? USA TODAY https://www.usatoday.com/story/news/health/2021/01/14/monoclonal-antibodies-covid-full-supply-but-lack-demand-hhs/4159950001/

716) 2021-01-15. U.S. Department of Health and Human Services: Monoclonal antibodies for high-risk covid positive patients combat. COVID.hhs.gov (First documented posting by on the Internet Archive (Wayback Machine) on January 15, 2021 which was the week of the delayed posting by the U.S. Copyright Office of Andrus CH: *1 Dear Mr President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020.* Registration Number / Date TX002232947 / 2020-11-18.) https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients

717) While this URL was the posting throughout from January 15, 2021 to the present (May18, 2021) the website has changed in information. The "combatCOVID.hhs.gov" website on January 15, 2021 can be found using the Wayback Machine of the Internet Archive: http://web.archive.org/web/20210115154152/https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients . This website is explicit DHHS qualitative rationing without justification and also implicit rationing as few Americans know to access this site:

> If you have COVID-19, you may be at high-risk of your symptoms getting worse. Based on your age, the length of your symptoms, and some medical conditions, you may be eligible for certain treatment or qualify for clinical studies.
>
> **WHAT IS A MONOCLONAL ANTIBODY?**
>
> Our bodies naturally make antibodies to fight infection. Monoclonal antibodies are made in a laboratory and are given to patients directly through an infusion. These treatments may help patients who are at high risk for severe illness avoid hospitalization and/or disease progression.
>
> COVID-19 monoclonal antibody treatments are different from COVID-19 vaccines. Vaccines provide active immunity by triggering the body's natural immune response. Vaccines often require two shots and time for the body to able to develop this immune response. When you have the virus, monoclonal antibody treatments give the antibodies that the body needs to protect itself.

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AM I A CANDIDATE FOR TREATMENT?

The FDA has authorized two monoclonal antibody treatments for emergency use bamlanivimab, casirivimab and imdevimab. These treatments could help the immune system respond more effectively to the virus. Your healthcare provider can help you determine if you're a candidate for treatment.

Monoclonal antibody treatments have been authorized by the FDA for patients who have tested positive for COVID-19 in the last ten days, who are 12 years of age and older, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

This also includes people who are 65 years of age or older or who have certain chronic medical conditions.

MILESTONE

Over 600,000 monoclonal antibodies have been distributed to healthcare facilities, nationwide.

DID YOU KNOW...

You're eligible to be treated with the monoclonal antibody if you are:

- 65 years of age or older
- 55 years or older with:
  - Heart disease
  - OR high blood pressure
  - OR COPD/chronic respiratory disease, including asthma.
- Any age with:
  - Obesity (a body mass index [BMI] of 35 or higher)
  - OR diabetes (Type 1 or Type 2)
  - OR chronic kidney disease
  - OR a weakened immune system
  - OR you're taking medicine that weakens your immune system.

Your child is eligible to be treated with the monoclonal antibody if he or she is:

- 12 to 17 years of age and at least 40 kg (88 pounds) with:
  - Obesity (a BMI greater than or equal to 85 percent of patients of the same age and gender)
  - OR regularly uses medical technology such as a ventilator or feeding tube
  - OR have a developmental condition like cerebral palsy
  - OR sickle cell disease
  - OR congenital or acquired heart disease
  - OR asthma/chronic respiratory problems requiring daily medication for control.

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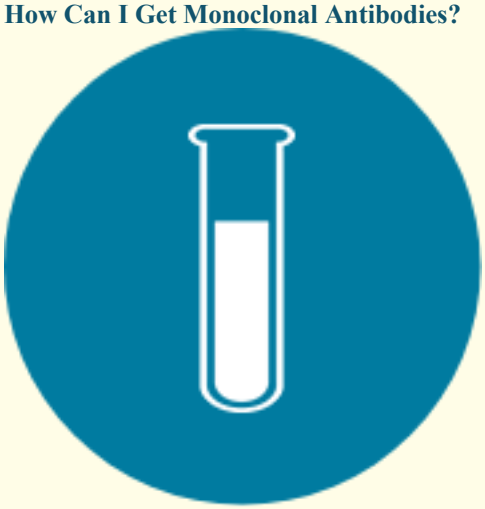
How Can I Get Monoclonal Antibodies?



Step 1: Test positive for COVID-19 in the last 10 days.

Step 2: Receive a referral from your healthcare provider.

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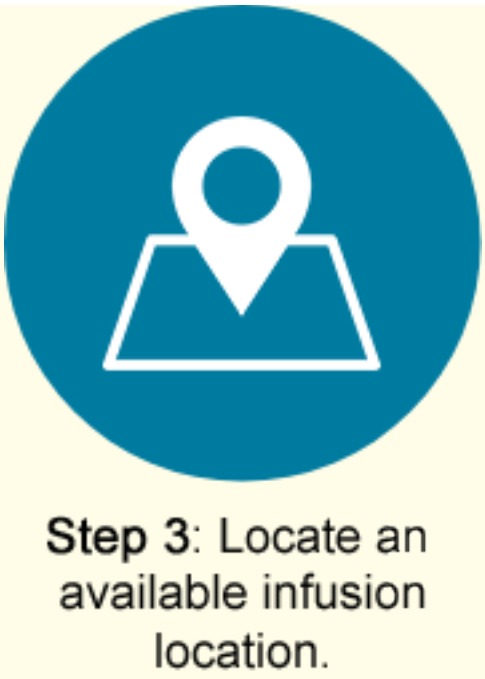

Patients who have had symptoms for 10 days or less should be referred for treatment by their healthcare providers and directed to available infusion locations.

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721) 2021-01-20 Fiore K: FDA Drowned in 'Junk Science'; sorting out COVID variants; Vax distributes chaos. MEDPAGE TODAY https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/90789

722) 2021-01-20 Perez E: Trump's acting attorney general leaves without creating controversial special counsels. CNN politics

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https://www.cnn.com/2021/01/20/politics/justice-department-special-counsel-rosen-wilkinson/index.html

723) 2021-01-21 Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocheria B, Stosor V, Shawa I, Kumar P, Adams AC, van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PH, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM: Effect of Bamlanivimabas monotherapy or in combination with Etesevimab on viral load in patients with mild or moderate COVID-19 A randomized clinical trial. JAMA. 2021;325(7):632-644.:10.1001/jama.20210202 https://jamanetwork.com/journals/jama/fullarticle/2775647

724) 2021-01-21 Cohen MS: Monoclonal antibodies to disrupt progression of early Covid-19 infection. N Engl J Med 384;3 NEJM.org January 21, 2021. https://www.nejm.org/doi/pdf/10.1056/NEJMe2034495?articleTools=true

725) 2021-01-21 Bump P: Fauci, unchained. https://www.washingtonpost.com/politics/2021/01/21/fauci-unchained/

726) 2021-01-21 Eli Lilly announcement to stockholders: Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. https://natap.org/2021/COVID/020321_02.htm

> INDIANAPOLIS, Jan. 21, 2021 /PRNewswire/ -- Bamlanivimab (LY-CoV555) significantly reduced the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities, Eli Lilly and Company (NYSE: LLY) announced. The Phase 3 BLAZE-2 COVID-19 prevention trial - conducted in partnership with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the COVID-19 Prevention Network (CoVPN) - enrolled residents and staff at skilled nursing and assisted living facilities, commonly referred to as nursing homes, across the U.S. The 965 participants who tested negative for the SARS-CoV-2 virus at baseline (299 residents and 666 staff) were included in the analysis of primary and key secondary endpoints for assessing prevention, while the 132 participants (41 residents and 91 staff) who tested positive for the virus at baseline were included in exploratory analyses for assessing treatment, adding to the growing body of evidence for treatment with bamlanivimab. All participants were randomized to receive either 4,200 mg of bamlanivimab or placebo.
>
> After all participants reached 8 weeks of follow-up, there was a significantly lower frequency of symptomatic COVID-19 (the primary endpoint) in the bamlanivimab treatment arm versus placebo (odds ratio 0.43, p=0.00021). Results for all key secondary endpoints also reached statistical significance in both the overall and resident populations.
>
> For the pre-specified subgroup of nursing home residents, there was also a significantly lower frequency of symptomatic COVID-19 in those treated with bamlanivimab versus placebo in this important population (odds ratio 0.20; p=0.00026). These results suggest that residents randomized to bamlanivimab have up to an 80 percent lower risk of contracting COVID-19 versus residents in the same facility randomized to placebo. Results from exploratory analyses of viral load in the treatment group were consistent with previously disclosed data from BLAZE-1

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evaluating bamlanivimab as an outpatient treatment for recently diagnosed COVID-19.

Among the 299 residents in the prevention group, there were 4 deaths attributed to COVID-19 at the time of death, and all occurred in the placebo arm. There were no COVID-19 attributed deaths in the bamlanivimab arm. Among the 41 residents in the treatment group, there were 4 deaths, and all occurred in the placebo arm with none in the bamlanivimab arm. Over the entire trial, there were a total of 16 deaths reported, including deaths not related to COVID-19, and all deaths were residents (11 deaths in placebo arm and 5 in bamlanivimab arm).

"We are exceptionally pleased with these positive results, which showed bamlanivimab was able to help prevent COVID-19, substantially reducing symptomatic disease among nursing home residents, some of the most vulnerable members of our society," said Daniel Skovronsky, M.D., Ph.D., Lilly's chief scientific officer and president of Lilly Research Laboratories. "These data provide important additional clinical evidence regarding the use of bamlanivimab to fight COVID-19 and strengthen our conviction that monoclonal antibodies such as bamlanivimab can play a critical role in turning the tide of this pandemic. We're glad bamlanivimab is already available as a treatment for patients at high risk for progressing to severe COVID-19 illness or hospitalization, including those in nursing homes, and look forward to working with regulators to explore expanding the emergency use authorization to prevent the spread of COVID-19 in these facilities."

Original announcement from Lilly of January 21, 2021: https://investor.lilly.com/node/44291/pdf

727) 2021-01-21 Kolata G: Drug prevents coronavirus infection in nursing homes, maker claims. The New York Times. https://www.nytimes.com/2021/01/21/health/coronavirus-eli-lilly.html

728) 2021-01-22 Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodríguez Y, Gallo JE, Salazar-Uribe JC, Santander MJ, Cala MP, Zapata W, Zapata MI, Manrique R, Pardo-Oviedo JM, Camacho B, Ramírez-Santana C, Anaya JM, the CP-COVID-19 group. COVID-19 convalescent plasma composition and immunological effects in severe patients. Journal of Autoimmunity 2021; 118: 1-16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7826092/pdf/main.pdf

729) 2021-01-23 Swaminathan A: BLAZE-1 Final publication: Monoclonal antibody cocktail Part II. https://rebelem.com/blaze-1-final-publication-monoclonal-antibody-cocktail-part-ii/

730) 2021-01-24 Face the Nation: Margaret Brennan interviews Deborah Birx, M.D. Face the Nation, CBSNews. The abridged version that aired on Face the Nation on Sunday morning, January 24, 2021: https://www.youtube.com/watch?v=odklJGnhvhU The complete interview of Dr. Birx by Margaret Brennan of Face the Nation of CBSNews: https://www.youtube.com/watch?v=nW41YylWipM

731) 2021-01-24 Kessler G, Rizzo S, Kelly M: Trump's false or misleading claims total 30,573 over 4 years. The Washington Post https://web.archive.org/web/20210125221959/https://www.washingtonpost.com/politics/2021/01/24/trumps-false-or-misleading-claims-total-30573-over-four-years/

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732) 2021-01-26 Frontline: Trump's American Carnage. Season 2021, Episode 3. https://www.pbs.org/video/trumps-american-carnage-cgbssm/

733) 2021-01-26 Lilly Investors New Release: New data show treatment with Lilly's neutralizing antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) together reduced risk of COVID-19 hospitalizations and death by 70 percent. https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies

734) 2021-01-29 Bodimer F: January 30th 2021 – Dr. Fred Buckhold, Dr. Bruce Hall, Dr. Rachel Presti & Katie Smith. https://www.audible.com/pd/January-30th-2021-Dr-Fred-Buckhold-Dr-Bruce-Hall-Dr-Rachel-Presti-Katie-Smith-Podcast/B08TH5Z7PR

735) 2021-01-31 Gray D: St. Louis hospital reports success using experimental COVID-19 Drug. KTVI https://www.news10.com/news/st-louis-hospital-reports-success-using-experimental-covid-19-drug/

736) 2021-02. Kaplan AP, Ghebrehiwet B: Pathways for bradykinin formation and interrelationship with complement as a cause of edematous lung in COVID-19 patients. J Allergy Clin Immunol 2021; 147: 507-509. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7598417/pdf/main.pdf

737) 2021-02-01 Oxford Vaccine Group: Vaccine Knowledge Project. https://vk.ovg.ox.ac.uk/vk/covid-19-vaccines

738) 2021-02-01 Andrus CH:

Dear Dr. Birx:

On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of ***Active Immunization*** (vaccines to stimulate patient antibody production) and ***Passive Immunization*** (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive).

In your interview with Margaret Brennan, you stated the following:

> DR. BIRX: Well, what I do know and what was reassuring to me all along is I knew this would be studied. I knew that the emails, the reports that I wrote, the request to expand testing, the **how to improve therapeutics**,

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all of that, all of that would eventually come to light. Maybe not in my lifetime.

Last summer you stated that we should collect 500,000 units of convalescent plasma to prepare for the spike in the Fall –well, we as a nation didn't do that. In fact, as you are a clinical Immunologist, you are very well aware of ***Passive Immunization*** in the initial early treatment (<72 hours) with the contraction of or exposure to a disease without any true alternate therapy as soon as possible (<72 hours) [e.g.: rabies, hydrops fetalis (Rhogam within 72 hours to an Rh negative mother at delivery of the prior **pregnancy**, snake bites, etc]. In fact, to withhold ***Passive Immunization*** (RhoGAM) from a newly delivered Rh negative mother is considered malpractice. By semantics and legal obfuscation, over the course of the last 10 months, the American public has been led down the rabbit hole by the Medical and Research community, the "Industry", and the Federal Government by not officially providing any timely-appropriate immunotherapy in the treatment of COVID-19 positivity with ***Passive Immunization*** until recently:

1. In March 2020, the FDA declared COVID-19 Convalescent Plasma *Investigational* instead of a *Biosimilar* biologic;

2. On March 24, 2020 the FDA outlined ***Eligibility Criteria*** in the late treatment of severe COVID-19 disease with COVID-19 Convalescent Plasma (at deaths door – when the viremia is not the cause of death but rather the SARS pathophysiology) justifying this choice of late administration as the US did not have enough recovered convalescent patients (>14 days) ;

3. In early April 2020, the Mayo Clinic with the FDA offered COVID-19 Convalescent Plasma in the Expand Access protocol Convalescent Plasma COVID-19 (Coronavirus) Treatment (uscovidplasma.org) using the at-deaths-door ***Eligibility Criteria*** ("expanded access" is really "compassionate use"—so, therefore, any resultant data cannot officially be used for completion of a Phase I Clinical Trial). Over 94,000 units of COVID-19 plasma were given AT THE THERAPEUTICALLY WRONG TIME only to severely-effected patients with the SARS pneumonitis or MSOF.

4. Throughout the last 11 months, the DHHS through the FDA and NIH has equated Safety Trials (Phase I trials) with Efficacy Trials (Phase II/III) so that there are no "Completed" Phase I (safety) trials with regards to COVID-19 biologics. Who should explain to the American people if the NIH plans on evading *ad infinitum* the "Right to Try" Law PL-115-176? Has not **a bad** precedent been set by not declaring a "completed" Phase I Trial with regards to COVID-19 Convalescent Plasma? Will any NIH protocol or FDA new drug/biologic Phase II/III trial and in any future research **not** be required to abide by the "Right to Try" Law, PL-115-176? In essence, the FDA and NIH are in violation, at least in violation of the intent of federal law PL-115-176 which requires a "Completed" Phase I Trial **only**

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for application of PL-115-176. Forcing patients to participate in Placebo-controlled Phase II/ III Trials is coercion which is prohibited by every IRB in the nation. On August 12, 2020 in the St. Louis Post-Dispatch, the following quote involving one of the FDA-Mayo Clinic's named investigators was documented:

> But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.
>
> "If you have a 50% chance of getting either the stuff or nothing, which would you choose?"
> https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_ccec0f56-4493-5a26-8601-45e35d364b2d.html

No IRB, worth their salt, should ever approve of such a concept of coercion in any Clinical Trial; and the FDA should not only shut down any Clinical Trial with such flagrant coercion but also censure, if not shut down, any IRB that permitted such coercion.

5. All summer, the FDA kept announcing they were close to releasing an EUA regarding COVID-19 Convalescent Plasma. President Trump went to the American Red Cross at the end of July confirming the need in his mind and that of the President's COVID-19 Taskforce for COVID-19 Convalescent Plasma. The announcement of the EUA was delayed until it would be announced on Sunday, August 23, 2020, by President Trump on the eve of the Republican National Convention. The next day, the NIH COVID-19 Guidelines Panel condemned the EUA for lacking scientific rigorous analysis (being based on Expanded Access/*Compassionate Use* protocol data from the FDA/Mayo clinic study). In the most-recent guidelines of the NIH COVID-19 Guideline Panel of January 14, 2021, the NIH COVID-19 Guidelines Panel is now hedging its bets by hiding under "Convalescent Plasma" *Last Update October 9, 2020*:

> Rationale for Recommendation
> Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. **The results of their analyses suggest that convalescent plasma with**

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> **high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.**

(While the Mayo Clinic's Expanded Access Program (EAP) did not have an official "untreated control arm" since it was *Compassionate Use* only, the Mayo Clinic's EAP Safety Update in June 2020 of 20,000 patients actually included a total of 21,987 infused patients with 1,987 patients not completing the post-infusion 7-day period and 8,130 being untreated. When one back-calculates varying the possible mortality rate in this untreated group, a mortality rate of 8.7% or greater would have been statistically significant with less than a 0.05% confidence level. *But, unfortunately, the Mayo Clinic's Expanded Access Program* did not even qualify as a "Completed Phase I Study" by the "purism" semantics of the NIH. Dr. Birx, the FDA has final statutory say over all new drugs and biologics, **NOT** the NIH.)

6. The Chief Scientist of the FDA, Rear Admiral Hinton, finally removed the severity criteria by removing completely the ***Eligibility Criteria*** regarding Remdesivir on August 28, 2020 (the VA Central Office pharmacy formulary panel was still insisting on the severity ***Eligibilty Criteria*** as the only criteria for those eligible for Remdesivir in November 2020--three months after it was rescinded by Rear Admiral Hinton). Veklury (remdesivir) EUA Letter of Approval, reissued 10/22/2020 (fda.gov)

7. On September 2, 2020, the FDA removed completely without public awareness the severe disease ***Eligibility Criteria*** for COVID-19 Convalescent Plasma. Many institutions are still applying the severe disease ***Eligibility Criteria*** to this day--thus refusing patients COVID-19 Convalescent Plasma treatment when they first become COVID-19 positive and present to the local ER—including recently a patient with a 104 fever and uncontrollable cough that I personally know. (i.e.: The FDA's complete removal of the ***Eligibility Criteria*** after September 2, 2020 can be demonstrated by viewing an example of the U.S. Food & Drug Administration's website: *Recommendations for Investigational COVID-19 Convalescent Plasma* by comparing the most recent URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma by copying and pasting the URL into the Internet Archive (Wayback Machine) and displaying a URL before September 2, 2020 in which the severe disease ***Eligibility Criteria*** was outlined from April 2020 to September 2, 2020: Recommendations for Investigational COVID-19 Convalescent Plasma | FDA (archive.org) :

> **Patient Eligibility**
>
> To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment ProtocolExternal Link Disclaimer. These criteria include:

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- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
    - Severe disease is defined as one or more of the following:
        - shortness of breath (dyspnea),
        - respiratory frequency ≥ 30/min,
        - blood oxygen saturation ≤ 93%,
        - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
        - lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening disease is defined as one or more of the following:
        - respiratory failure,
        - septic shock,
        - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

8. Before the EUAs were issued by Rear Admiral Hinton regarding the Regeneron monoclonal cocktail (casirivimib and imdevimab) and Eli Lilly monoclonal antibody bamlanivimib, on October 26, 2020 Eli Lilly asked the FDA to exclude the use of their monoclonal antibody in patients with any signs of severity of associated illness parameters such as any new requirement of oxygen supplementation in any non-COPD patient or increase in amount of oxygen supplementation in COPD patients.

9. Rear Admiral Hinton issued EUAs for Eli Lilly's bamlanivimib (https://www.fda.gov/media/143602/download) on November 10, 2020 and for Regeneron's casirivimib and imdevimab on November 21, 2020 (https://www.fda.gov/media/143891/download). Both EUAs state the following (I will use the Regeneron's monoclonal cocktail as the example as President Trump had received this "experimental" cocktail in early October 2020 prior to the issuing of these EUAs):

> **II. Scope of Authorization**
>
> I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:
>
> > • Distribution of the authorized casirivimab and imdevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor(s)4, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;
> >
> > • The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
> >
> > • Casirivimab and imdevimab may only be administered together;
> >
> > • **Casirivimab and imdevimab is not authorized for use in the following patient populations [5]:**

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• Adults or pediatric patients who are hospitalized due to COVID-19, or
• Adults or pediatric patients who require oxygen therapy due to COVID19, or
• Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

• Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

• The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

10. On November 24, 2020, in *NEJM* was published: Simonovich VA, *et al*: A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia (nejm.org) which is an outstanding, well-thought-out prospective trial using the discontinued/withdrawn severely-ill COVID-19 patient ***Eligibility Criteria*** in which all COVID-19 Convalescent Plasma was given only in patients with severe COVID-19 SARS pneumonitis. Unfortunately, the authors failed to mention in their paper's abstract conclusion that the outcome of the study was based on patients given COVID-19 Convalescent Plasma with only severe SARS pneumonitis—following the previously omitted (September 2, 2020) severe patient ***Eligibility Criteria*** in which ***Passive Immunization*** was administered at the WRONG TIME—that is at deaths-door instead of within 72-hours of COVID-19 positivity!:

> CONCLUSIONS
> No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, **NCT04383535. opens in new tab**.)

11. I wrote a Letter to the Editors of *The New England Journal of Medicine (NEJM)* regarding Simonovich VA, *et al* and included those I could access with regards to e-mails in the DHHS, the VA, and Saint Louis University SOM as I am a Professor of Surgery and the General Surgery Residency site director at the St. Louis (John Cochran) VAMC. I never got a response back from the *NEJM* but on January 6, 2021, the landmark article by Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) demonstrated a statistically significant decrease in mortality and severity of illness in a specific age group (the elderly) when COVID-19 Convalescent Plasma was given within 72 hours **(AT THE RIGHT TIME)** of detection of COVID-19 positivity. As is stated in the conclusion of the abstract in this article:

> CONCLUSIONS
> Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of

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Covid-19. (Funded by the Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund; Dirección de Sangre y Medicina Transfusional del Ministerio de Salud number, PAEPCC19, Plataforma de Registro Informatizado de Investigaciones en Salud number, 1421, and ClinicalTrials.gov number, NCT04479163.)

One of my fellow Attending Surgeons at the VA came to my office after my e-mail cover letter to my Letter to the Editors to *NEJM* and stated that I had every right under the first Amendment to communicate whatever I wished but I was just making a fool of myself as there were much smarter people than me involved in setting standards for COVID-19 therapy. The next night, I got a call from an administrator at Saint Louis University SOM (SLUSOM) stating I was only allowed to speak about COVID-19 Convalescent Plasma with other faculty members of SLUSOM and the physicians, nurses, and other healthcare personnel at the local VA--St. Louis (John Cochran) VAMC and to STOP calling Washington DC. He then asked me unknowingly why I had included e-mails to Harvard. I responded that this e-mail was concerned my cover letter regarding my letter to the Editors of *The New England Journal of Medicine*. He responsed: Oh—speak only with those in the local VA and Saint Louis University.

[Please note I attached a slide of mortality due to COVID-19 by age range between March and November 2020. First, the mortality percentages by age range had not changed over those 9 months suggesting the USA has not diminished the death rate by any therapy employed so far in any age group over 40 years of age. Second, you will note, the mortality from 40 to 90 years increases by 0.67% per year: $y= 0.0067x – 0.2647$, $R^2= 0.9676$; and, below age 40, the mortality rate increases only by 0.04% per year to maximally 0.12%/year: $y= 0.0004x – 0.0023$, $R = 0.7987$. Once again, as the mortality rates in all range groups over the age of 40 have not changed over the last 10 months, the late administration of ***Passive Immunization*** to the majority of the hundred thousand patients that received COVID-19 Convalescent Plasma was given at the WRONG TIME using the now rescinded FDA patient ***Eligibility Criteria***--such administration at the WRONG TIME did not make a substantial impact. What this also implies is that sending the children and young adults back to in-school-learning will be relatively safe for the children—mortality rate 0.04% increase per year when compared with adults over age 40 years—mortality rate 0.67% per year (which is 16x higher than in children). This presents the possibility to generate a vector repository in our children who could then transmit COVID-19 to their parents, grandparents, and other adults who have a higher risk of severity of disease and death.]

12. The *NEJM* landmark article of January 6, 2021 by Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) was overshadowed by the events that occurred later in the day in Washington

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D.C. Ironically, on January 14, 2021, *USA Today* ran an article: Rodriguez A: US officials urge Americans to ask their doctors about monoclonal antibodies for COVID. But is it too little, too late? Monoclonal antibodies for COVID in full supply, but lack demand: HHS (usatoday.com) . On January 17, 2021 in *Infection Control* Today, Kavanagh K: As Vaccine Rollout Stalls, Move Monoclonal Antibodies Into COVID Fight (infectioncontroltoday.com) using monoclonal antibodies used prophylactically to protect in exposures. **Both** monoclonal antibodies and COVID-19 Convalescent Plasma are ***Passive Immunization*** therapeutic agents and should therefore be administered at the same appropriate time-- <72 hours from symptomatology or COVID-19 positivity instead of only to patients at deaths-door. Over the last 10 months, the American public has been so misdirected (or lied to) by the ambiguity in the terminology and focus on vaccine production that few realize that ***Passive Immunization*** includes polyclonal antibodies (COVID-19 Convalescent Plasma) and monoclonal antibodies which should be given to all immediately when they become COVID-19 positive!

13. As is now being reported in the press, mutations of COVID-19 are developing around the World that may make the present vaccines and monoclonal antibodies ineffective.

14. As we go forth, the Standard-of-Care should be the following:

    A. For those of the present 330 million Americans that are not yet infected (immunologically naïve to the disease – COVID-19 negative), they should all be encouraged to receive one of the COVID-19 vaccines.

    B. Every American who has had COVID-19 and is recovered by at least 14 days should be encouraged to donate COVID-19 Convalescent Plasma. https://www.aabb.org/for-donors-patients/give-blood

    C. Every American who turns COVID-19 positive or becomes symptomatic (even if they have received a COVID-19 vaccine), should be afforded some form of ***Passive Immunization*** by the early-in-disease treatment COVID-19 Convalescent Plasma/Sera or Monoclonal Antibiodies

    D. As the COVID-19 mutations spread and the vaccines may be less effective, every American who turns COVID-19 positive or becomes symptomatic should be afforded ***Passive Immunization*** of COVID-19 Convalescent Plasma/Sera matching the COVID-19 mutation. Waiting for the development of a vaccine (or monoclonal antibodies) specific for the new COVID-19 mutation and withholding mutation specific COVID-19 Convalescent Plasma would be unconceivable and tantamount to patient

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abandonment. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation.

E. When Kidney Transplantation was considered *Investigational* in the 1960s and 1970s and the insurance industry would not pay for Kidney Transplantation as it was "Experimental", the Congress permitted for two decades the Attending Surgeons of Washington University SOM (Drs. Newton and Anderson) and Saint Louis University SOM (Drs. Maginn, Codd, and Garvin) to perform kidney transplants on both Veterans and civilians at the John Cochran (St. Louis) VAMC. Thus, the precedent six decades ago was set to employ the largest federal hospital system (both hospitals and CBOCs) in the nation of the Veterans Health Administration (VHA) to establish infusion centers to provide ***Passive Immunization*** in the treatment of COVID-19 for both Veterans and civilians.

F. Thomas Jefferson's replacement of John Locke's "property" with "the pursuit of happiness" in the *Declaration of Independence* was no mistake. We as American physicians should be leery of any potential inherent conflict-of-interest of *Industry's* and *Medicine's* working together possibly to the detriment of our patients. *De facto,* Medicine, the U.S. Government, and most of the World have publicly discredited polyclonal COVID-19 Convalescent Plasma (and Sera) while elevating monoclonal antibodies as viable early treatments in COVID-19 positivity—they are both ***Passive Immunization*** therapies. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation. The present situation throughout the World today is analogous to that of the mythological Sisyphus pushing the rock up the hill only for it upon nearing the top of the hill rolling back down for eternity.

After having viewed the abridged version of your interview on January 24, 2020 (Full interview: Dr. Deborah Birx on "Face the Nation" - YouTube) with Margaret Brennan, in my eyes you have throughout your professional life been a dedicated Military and Civil Service physician for individual patients and patients in the aggregate. Both you and I are professionally of the same generation. When we graduated, you from Penn State Univ SOM in 1980 and I in 1979 from Saint Louis Univ SOM, we both swore *Primum non Nocere* in the care of all of our patients throughout our future lives as physicians. As I viewed the interview last Sunday, I saw a physician who loves her country and has dedicated her life as a physician to bettering all patients' lives. It is

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your duty, my duty, and all physicians' duty by our oaths of *Primum non Nocere* to advocate for not just the preventative measures of ***Active Immunization*** but also all potential therapeutic measures of ***Passive Immunization***.

It would be my hope that this correspondence will be your introduction to President Biden to explain your suggestions and thoughts on our future therapy—**both *Active Immunization* and *Passive Immunization***-- for all Americans. As Dr. Fauci is the President's Chief Medical Advisor on the USA COVID-19 epidemic, I will forward this letter to him, the NIH, and the FDA to help facilitate your meeting with the President. My previous Letter to the Editor of *The New England Journal of Medicine* has not been published but was probably partially the impetus for the *NEJM* publishing on January 6, 2021-01-06: Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) I will be sure to include the Editors of the *New England Journal of Medicine* in this correspondence today. Over the past year, I have submitted three items (listed below) to the U.S. Copyright Office of the Library of Congress to preserve the chronology of what has occurred for history. With any and all of my correspondence regarding our present COVID-19 epidemic, I will dutifully provide all that is asked of me by the U.S. Federal Government as it is my duty as a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs.

1. Andrus CH: *Time*: The Crucial Independent Variable of the COVID-19 Pandemic. U.S. Copyright Office, June 8, 2020. TXu002199029

2. Andrus CH: Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. July 22, 2020. TXu002214049

3. Andrus CH: 1 Dear Mr. President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. November 18, 2020. TXu002232947

On the evening of January 20, 2021, the America public was reminded of past Presidential inaugural addresses:

President Abraham Lincoln's 2nd Inaugural Address includes the lines that I, as a VA physician and surgeon, and we as Americans have promised:

> With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; **to care for him who shall have borne the battle, and for his widow, and his orphan**; to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

That night, the most famous line of President Kennedy's was part of what was recited: "And so, my fellow Americas: ask not what your country can do for you—ask what you can do for you country." Dr. Birx, both you and I were in grammar school when the final lines were spoken that are most *apropos* to our present crisis and that for all time:

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

> My fellow citizens of the world: ask not what America will do for you, but what together we can do for the freedom of man.
>
> Finally, whether you are citizens of America or citizens of the world, ask of us here the same high standards of strength and sacrifice which we ask of you. With a good conscience our only sure reward, with history the final judge of our deeds, let us go forth to lead the land we love, asking His blessing and His help, but knowing that here on earth God's work must truly be our own.

Dr. Birx: Godspeed.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine
Chief, Unit II General Surgery (SLU GS division), St. Louis (John Cochran division) VAMC

Home: 314-455-9482; home e-mail: candrus600@aol.com
Beeper: 314-491-2417
My wife's, Pamela Bergkamp Andrus's, cell phone: 314-809-9634

739) 2021-02-02 U.S. Food & Drug Administration: CLINICAL MEMORANDUM, EUA 26382, COVID-19 Convalescent Plasma (CCP). NONE OF THE VERSIONS OF THESE MEMOs are dated and thus dating was obtained from the digital captures using the Internet Archive (WayBack Machine). The URL of this Memorandaum is: https://www.fda.gov/media/141480/download

From September 1, 2020 to at least February 2, 2021 was <u>the first iteration/rough draft</u> to justify Hinton's reissuing the CCP EUA in November 2020 and then probably (the Wayback Machine has no digital captures from Feb 2 to Feb 15) the first major revision on February 4, 2021, of the CCP EUA of August 23, 2020 which was the first EUA regarding COVID-19 Convalescent Plasma issued by the FDA after the press conference announcement by President Trump of that day: Sunday, August 23, 2020—the day prior to the start of the Republican National Convention. Coincidentally, this **six-month draft** was the CLINICAL MEMORANDUM probably used to justify RADM Hinton's EUA of February 4, 2021 which was 48-72 hours after Dr. Andrus' Letter to Dr. Deborah Birx of February 1, 2021. As this first iteration of the MEMO regarding EUA 26382 was a draft, it lacks (1) the name of the individual who wrote it; (2) the name of the individual to whom it is written; and (3) the names of the FDA division chiefs through which the memo would pass. It does list the Sponsor, Robert Kadlec, M.D., to whom all EUAs previously have been issued regarding Remdesivir, Monoclonal Antibodies/Antibody Cocktails, and COVID-19 Convalescent Plasma (CCP). https://web.archive.org/web/20210202143902/https://www.fda.gov/media/141480/downl

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

oad The Executive Summary of the CLINICAL MEMORANDUM of September 1, 2020 through at least February 2, 2021:

> EXECUTIVE SUMMARY COVID-19 Convalescent Plasma (CCP), an unapproved biological product, is proposed for use under an Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act),(21 USC 360bbb-3) as a passive immune therapy for the treatment of hospitalized patients with COVID-19, a serious or life-threatening disease. There currently is no adequate, approved, and available alternative to CCP for treating COVID-19. The sponsor has pointed to four lines of evidence to support that CCP may be effective in the treatment of hospitalized patients with COVID-19: 1) History of convalescent plasma for respiratory coronaviruses; 2) Evidence of preclinical safety and efficacy in animal models; 3) Published studies of the safety and efficacy of CCP; and 4) Data on safety and efficacy from the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.
>
> Considering the totality of the scientific evidence presented in the EUA, I conclude that current data for the use of CCP in adult hospitalized patients with COVID-19 supports the conclusion that CCP meets the "may be effective" criterion for issuance of an EUA from section 564(c)(2)(A) of the Act. It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the course of disease. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for its use.
>
> **Recommendation:** CCP meets the eligibility criteria for EUA under section 564 of the Act.

February 15, 2021 was the first digital capture of <u>the second interation</u> to justify the ongoing EUAs of COVID-19 Convalescent Plasma (CCP) upgrades by RADM Hinton. As this second iteration of the MEMO regarding EUA 26382 does not seem to be a draft, it contains (1) the name of the individual who wrote it; (2) the name of the individual to whom it is written; and (3) the names of the FDA divisions chiefs through which the memo would pass. It does not list the Sponsor (not yet appointed by the Biden administration and confirmed) to whom all EUAs will be issued regarding Remdesivir, Monoclonal Antibodies/Antibody Cocktails, and COVID-19 Convalescent Plasma (CCP).
http://web.archive.org/web/20210215192634/https://www.fda.gov/media/141480/download The Executive Summary of the CLINICAL MEMORANDUM from February 15, 2021 to at least April 23, 2021 (the last digital capture by the WayBack Machine) to be unchanged:

> **EXECUTIVE SUMMARY**
>
> COVID-19 Convalescent Plasma (CCP) was granted Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 on August 23, 2020. At that time, the totality of the scientific evidence supported a determination that the use of CCP in hospitalized patients with COVID-19 met the "may be effective" standard for issuance of an EUA, and it was reasonable to consider that the known and potential benefits of CCP outweighed the known and potential risks for the authorized use.

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Following the EUA, emerging evidence from randomized controlled trials has continued to inform this assessment. The available evidence indicates that 1) the use of low titer CCP in hospitalized patients no longer meets the evidentiary standard of "may be effective", and 2) high titer CCP has not demonstrated benefit when administered late in the disease course in immunocompetent hospitalized patients.

Additional data from RCTs and observational studies support a determination that high titer CCP may be effective when administered early in the course of illness, particularly prior to the expected time of host antibody response. In patients with impaired humoral immunity, the potential therapeutic window may be prolonged. As RCT data continue to demonstrate that the risks of CCP do not exceed those observed with plasma transfusion in general, it is reasonable to believe that the known and potential benefits of use of high titer CCP outweigh the known and potential risks when used for the treatment of hospitalized patients with COVID-19, particularly early in the course of illness or in patients with impaired humoral immunity. Results from ongoing RCTs are expected to continue inform the optimal patient populations and product characteristics for efficacy of CCP in COVID-19.

Recommendation: *The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization.* The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product characteristics meeting EUA criteria.

740) 2021-02-04 Hinton DM: U.S. Food and Drug Administration Letter to Nikki Bratcher-Bowman, Acting Assistant Secretary for Preparedness and Response, EUA-update regarding COVID-19 Convalescent plasma. February 4, 2021. (Please note that the position of Assistant Secretary of Preparedness and Response changed from February 2, 2021 (48 hours previous) from Robert Kadlec, M.D. who had been appointed by President Trump to an Acting Assistant Secretary for Preparedness and Response under the Biden Administration: Nikki Bratcher-Bowman.)
https://web.archive.org/web/20210218201225/https://www.fda.gov/media/141477/download

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2).[1] On March 27, 2020, on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to the terms of any authorization issued under that section.[2] On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), pursuant to Section 564 of the Act.[3] On November 30, 2020, FDA reissued the August 23, 2020, Letter of Authorization to add a test acceptable to be used in the manufacture of COVID-19 convalescent plasma.[4] Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), **FDA is again reissuing the Letter of Authorization in its entirety with revisions**

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to: (1) include updates based on data from additional clinical trials; **(2) clarify that the authorization is limited to use of only high titer COVID-19 convalescent plasma in hospitalized patients early in the course of disease and those hospitalized with impaired humoral immunity;** (3) add the Abbott SARS-CoV-2 IgG test (ARCHITECT and Alinity i platforms), Beckman Coulter Access SARS-CoV-2 IgG test, EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) test, GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit test, Kantaro COVID-SeroKlir test, Roche Elecsys AntiSARS-CoV-2 S test, and Siemens ADVIA Centaur SARS-CoV-2 IgG (COV2G) test as acceptable tests to be used for the purpose of qualifying high titer COVID-19 convalescent plasma in the manufacture of COVID-19 convalescent plasma; and (4) change the cutoff of the Ortho VITROS Anti-SARS-CoV-2 IgG test from S/C≥12.0 to S/C≥9.5 for qualification of COVID-19 convalescent plasma as high titer. COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. It is an investigational product and is not currently approved or licensed for any indication. The initial issuance of this EUA for COVID-19 convalescent plasma was based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic. [5] Following the August 23, 2020 authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 convalescent plasma, and further characterize product attributes and patient populations for its use. Based on assessment of these data, potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease. [6] Transfusion of COVID-19 convalescent plasma in hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit. These considerations may be different in patients with suppressed or deficient humoral immunity. **Therefore, this EUA is being revised to authorize only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the disease course.** The related fact sheets are revised accordingly. The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA.

It is reasonable to believe that the known and potential benefits of high titer COVID-19 convalescent plasma outweigh its known and potential risks for the treatment of patients hospitalized with COVID-19 early in the disease course.[7] COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Given that the clinical evidence supporting this EUA remains limited, data from additional randomized, controlled trials are needed. Ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this updated EUA; providers are encouraged to enroll patients in those trials. Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of high titer COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

741) 2021-02-04 U.S. Food & Drug Administration: FDA in Brief: FDA Updates Emergency Use Authorization for COVID-19 Convalescent Plasma to Reflect New Data, February 4, 2021. **This is deliberate legal obfuscation on the part of the FDA by stating that it was limiting authorization-- *de facto,* the FDA was really expanding authorization by appropriately limiting the EUA for COVID-19 Convalescent Plasma to *"early in the disease course"* which was contrary to FDA directives from March 24, 2020 to**

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September 2, 2020 when the criteria was that CCP could *only* be given to severe patients late in the disease course. The provision of CCP late in the disease course was *de facto* perpetuated by the fact that the FDA had unobtrusively removed the strict severity of illness criteria late in the disease course from all FDA documentation by overwriting on September 2, 2020 and going forward on all subsequent documentation and not announcing it *officially* to the U.S. Medical and Research Community, probably the rest of the Federal Government, and most definitely not to the American people. The "high dose" vs "low dose" concern is a secondary issue—that was used as a distraction by the FDA--as with monoclonal antibodies/antibody cocktails, COVID-19 Convalescent Plasma and monoclonal antibodies are all *Passive Immunization* and are therapeutically identical if given ***EARLY IN THE COURSE OF THE DISEASE.*** https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-emergency-use-authorization-covid-19-convalescent-plasma-reflect-new-data

The following quote is attributed to **Peter Marks, M.D., Ph.D., Director of FDA's Center for Biologics Evaluation and Research**:

> **"The FDA is issuing a revision of the Emergency Use Authorization (EUA) for COVID-19 convalescent plasma as a result of our evaluation of the most recent information available. Based upon data from new clinical trials analyzed or reported since the original EUA was issued in August 2020, we have revised the EUA to limit the authorization to the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course. This and other changes to the EUA represent important updates to the use of convalescent plasma for the treatment of COVID-19 patients.**
>
> **"Issuance of, and updates to, EUAs are based on a thorough evaluation of currently available scientific evidence about medical products. In this case, as additional scientific evidence about COVID-19 convalescent plasma emerged, we revised the EUA to reflect the updated evidence. COVID-19 convalescent plasma used according to the revised EUA may have efficacy and its known and potential benefits outweigh its known and potential risks."**

742) 2021-02-04. Cox D: The vaccine alternatives for people with compromised immune systems. National Geographic Science – Coronavirus. February 4, 2021. https://www.nationalgeographic.com/science/article/the-vaccine-alternatives-for-people-with-compromised-immune-systems

743) 2021-02-04 Roxby P: Covid: 'Convalescent plasma no benefit to hospital patients.' British Broadcasting Corporation (BBC) https://www.bbc.com/news/health-55681051

744) 2021-02-05 REGENERON: Regeneron reports fourth quarter and full year 2020 financial and operating results. https://investor.regeneron.com/news-releases/news-release-details/regeneron-reports-fourth-quarter-and-full-year-2020-financial

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745) 2021-02-05 Yoon D: Enthusiasm fades for Covid-19 antibody treatments in South Korea – 'We are hoping the treatment will lighten the burden of hospitalizing patients with serious symptoms'. The Wall Street Journal, Feb. 5, 2021 7:02 am ET. https://www.wsj.com/articles/enthusiasm-fades-for-covid-19-antibody-treatments-in-south-korea-11612526555

746) 2021-02-05 Dockser Marcus A: FDA Limits Use of Convalescent Plasma as Covid-19 Treatment. Agency to scale back authorization of the antibody-rich blood component after studies yielded mixed results. The Wall Street Journal Feb 5, 2021. https://www.wsj.com/articles/fda-limits-use-of-convalescent-plasma-as-covid-19-treatment-11612537239

[This article is copied verbatim from the Wall Street Journal with annotations so as to translate what is meaningfully being said by those interviewed!].

The Food and Drug Administration is scaling back its authorization of the use of convalescent blood-plasma for Covid-19 patients in an effort to guide physicians who have faced a confusing thicket of data about the therapy's effectiveness.

The agency said late Thursday that the authorization, a subject of controversy since it was first issued last August, would be revised to limit the use of plasma to **hospitalized patients** *early in the course of the disease* and **hospitalized patients with a medical condition that impairs their ability to make antibodies.** Patients will be allowed to receive ***only plasma containing high concentrations of antibodies.***

"The update is meant so convalescent plasma can best be used on those who will benefit," said Peter Marks, director of the FDA's Center for Biologics Evaluation and Research. "It is being used somewhat more indiscriminately." ***[High-titer COVID-19 Convalescent Plasma should be given to everyone becoming COVID-19 positive within <72 hours. – NOT just those hospitalized.—C. Andrus]***

Dr. Claudia Cohn, chief medical officer of AABB, an organization representing the transfusion-medicine community, said the group plans to issue interim recommendations on convalescent plasma later this month. "There are so many studies coming out with different conclusions," she said. "It is not clean, it is not black and white."

Dr. Marks said the FDA reached its decision after evaluating results from several recent studies. Some showed benefits from convalescent plasma, the antibody-containing fluid derived from the blood of people who have recovered from Covid-19. Others showed no benefit.

Two clinical trials of convalescent plasma for hospitalized patients shut down last month after investigators said there appeared to be no benefit. Three trials involving hospitalized patients recently reported some benefit for the plasma, but only when given to patients soon after admission. **Still another trial showed that elderly outpatients given plasma shortly after showing symptoms were less likely to develop serious disease. ----** ***[This was the January 6, 2021 publication in The New England Journal of***

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Medicine which is the <u>ONLY</u> Prospective randomized, placebo controlled trial of CCP administration in one cohesive age group (~70 years of age). THIS IS A LANDMARK STUDY! – C. Andrus]

Arturo Casadevall, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, called the FDA decision "a step forward." He said, "Physicians in the U.S. for the first time are going to have guidance on when to use it and how to use" convalescent plasma.

Dr. Casadevall is a co-founder of the Covid-19 Convalescent Plasma Project, which helped organize a nationwide expanded-access study of convalescent plasma that began last April.

Despite the contradictory findings, convalescent plasma remains in demand—in part because there are few effective treatments for Covid-19 and many people remain unvaccinated. Since the FDA issued the emergency authorization last August, the blood industry has distributed on average about 20,600 units of convalescent plasma a week to hospitals around the country, according to the American Red Cross.

The FDA's earlier decision to authorize convalescent plasma for hospitalized Covid-19 patients was based in large part on results from an agency-sponsored expanded-access program, through which more than 72,000 patients received plasma. For a study published last month in the New England Journal of Medicine, researchers analyzed data from 3,000 of those patients and reported an apparent survival benefit among hospitalized patients not on mechanical ventilation who received plasma containing high concentrations of antibodies.

But many scientists expressed skepticism about that finding, saying expanded-access studies lack the scientific rigor of traditional trials because they have no control group to compare any apparent effect.

The FDA's Dr. Marks said the authorization of convalescent plasma "could have been handled much better. It had to do with the sense of urgency everyone is feeling. I can't blame anyone for feeling a sense of urgency." -- ***[As Dr. Marks is the Director of the FDA's CBER (Center for Biologics Evaluation and Research), it was <u>his sole responsibility to have handled it better</u> from March 2020 to the present for the biologic: COVID-19 Convalescent Plasma which is a biosimilar biologic to rabies vaccine, gamma globulin, RhoGam, hypertet, small pox convalescent plasma, IVIG, FFP, etc., etc., etc!]***

Dr. Marks also said the data could be confusing. Each unit of convalescent plasma is unique, reflecting the immune response of the recovered patient who donated it. It took time to figure out the best way to measure the antibodies in a unit, he added.

The U.S. isn't the only government trying to establish reliable guidelines on the use of convalescent plasma. In Argentina, a study in elderly outpatients published last month in the New England Journal of Medicine contributed to current recommendations there to treat elderly Covid-19 patients early in the course of their illness. "Plasma supplies are not endless, and invariably public health officials face difficult decisions," said study co-author Dr. Fernando Polack of

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Fundación Infant in Buenos Aires. “In any of these decisions, guidelines based on data are necessary and are the best way for clinicians to feel comfortable when facing individual cases.”

Louis M. Katz, chief medical officer of Mississippi Valley Regional Blood Center in Davenport, Iowa, which provides blood products for over 120 hospitals, said the evidence supporting the use of convalescent plasma in hospitalized patients is weak. **“I think the data is there that it works early,” he said. “As you move into sicker and sicker people, the evidence gets thinner and thinner.”**

In an editorial that accompanied the New England Journal of Medicine paper on the U.S. expanded-access study, **Dr. Katz said convalescent plasma should be used only in patients early in the course of the disease. The problem with that suggestion, he later added, is the FDA emergency-use authorization still covers only hospitalized patients, who tend to show up at the hospital when they have been sick for a longer time. *– [This is the problem, to become hospitalized, most patients have to be very sick and thus outside the <72 hour window! – C. Andrus, M.D.]***

Treating Covid-19 patients who are just starting to show symptoms poses its own challenges. “Logistically, it is very difficult to treat patients earlier,” Dr. Katz said**. “It’s hard to transfuse lots of plasma in outpatients.” *[BUT IT CAN BE DOWN IN INFUSION CENTERS or Hospital outpatient centers as is done for all infusion chemotherapies, chronic blood transfusions, etc! – C. Andrus. M.D.]***

Dr. Marks said a large National Institutes of Health study is now under way to test convalescent plasma in people with Covid-19 who are sick enough to come to the emergency room but aren’t admitted to the hospital, as are other randomized controlled trials of plasma in outpatients. “Until we have those data, we are going to keep the authorization to hospitalized patients,” he said. **“We will refine it again if appropriate. This is a scarce resource.” *[High-titer COVID-19 Convalescent Plasma should NOT be a scarce resource as it can be obtained twice a week from the same convalescent donor by PLASMAPHORESIS and the product from each donation will yield 2 doses (4 doses per week) and it can be stored as FFP (Fresh Frozen Plasma) for at least a year! In short, there are over 5,000 blood banks in the US so if each Blood Bank processed 20 units a day of COVID-19 Convalescent Plasma, that would be:***

20 donations / day times ***7 days/week*** times ***>5000 U.S. Blood Banks*** times ***2 doses of CCP / donation = greater than 1.4 million doses per week of CCP***

– C. Andrus, M.D.]

Write to Amy Dockser Marcus at amy.marcus@wsj.com
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Appeared in the February 6, 2021, print edition as 'FDA Limits Plasma as Treatment.'

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747) 2021-02-06 Mershon M: Austin regional infusion center makes it easier for COVID-19 patients to get antibody therapy. https://spectrumlocalnews.com/tx/austin/news/2021/02/05/austin-regional-infusion-center-makes-it-easier-for-covid-19-patients-to-get-antibody-therapy

748) 2021-02-09 Kaka AS, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, Wilt TJ: Major Update: Remdesivir for Adults with COVID-19 – A living systematic review and meta-analysis for the American College of Physicians practice points. Ann Internal Med https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7901604/pdf/aim-olf-M208148.pdf

749) 2021-02-09 Hinton DM: Emergency Use Authorization 090 regarding Eli Lilly's bamlanivimab. U.S. Food & drug, February 9, 2021. http://web.archive.org/web/20210210103943/https://www.fda.gov/media/143602/download

750) 2021-02-09 Hinton DM: Emergency Use Authorization 094 regarding Eli Lilly's bamlanivimab and etesevimab. U.S. Food & drug, February 9, 2021. https://web.archive.org/web/20210210011139/https://www.fda.gov/media/145801/download

751) 2021-02-09 Food and Drug Administration: Coronavirus (COVID-19) update: FDA authorizes monoclonal antibody for treatment of COVID-19. FDA news release, February 09, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0

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756) 2021-02-10 Andrus C: Use of COVID-19 convalescent plasma EARLY in the course of the disease. ResearchGate https://www.researchgate.net/post/Use_of_COVID-19_Convalescent_Plasma_EARLY_in_the_course_of_the_disease

757) 2021-02-11 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. February 11, 2021. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

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These is verbatim from the February 11, 2021, NIH Recommendations.

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

In the earliest stages of infection, before the host has mounted an effective immune response, anti-SARS-CoV-2 antibody-based therapies may have their greatest likelihood of having an effect. In this regard, although there are insufficient data from clinical trials to recommend either for or against the use of any specific therapy in this setting, preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies for the treatment of outpatients with mild to moderate COVID-19; please see Anti-SARS-CoV-2 Monoclonal Antibodies for more information.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.[1-4]

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.[5-8]

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The COVID-19 Treatment Guidelines Panel (the Panel) continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. Figure 1 summarizes the Panel's recommendations for managing patients with varying severities of disease.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnote.

DISEASE SEVERITY
PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19
There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression.[a]
The Panel recommends against the use of dexamethasone or other corticosteroids (AIII).[b]
Hospitalized but Does Not Require Supplemental Oxygen
The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).[b]
There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen
(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)
Use one of the following options:
• Remdesivir[c,d] (e.g., for patients who require minimal supplemental oxygen) (BIIa)
• Dexamethasone[e] plus remdesivir[c,d] (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII)[f,g]
• Dexamethasone[e] (e.g., when combination therapy with remdesivir cannot be used or is not available) (BI)
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation
Use one of the following options:
• Dexamethasone[e,g] (AI)
• Dexamethasone[e] plus remdesivir[c,d] (BIII)[f,g]
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO
Dexamethasone[e] (AI)[h]
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion
[a] See the Anti-SARS-CoV-2 Monoclonal Antibodies section for more information on using bamlanivimab and casirivimab plus imdevimab in patients with mild to moderate COVID-19.
[b] Patients who are receiving corticosteroids for other indications should continue therapy for their underlying conditions as directed by their health care providers.
[c] The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[e] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
[f] The combination of dexamethasone and remdesivir has not been studied in clinical trials.
[g] In the rare circumstances where corticosteroids cannot be used, baricitinib plus remdesivir can be used (BIIa). The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.
[h] The combination of dexamethasone and remdesivir may be considered for patients who have recently been intubated (CIII). The Panel recommends against the use of remdesivir monotherapy in these patients.
Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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759) 2021-02-11 U.S. Food & Drug Administration: Investigational COVID-19 convalescent plasma – Guidance for Industry. February 11, 2021 supersedes that issued January 15, 2021. https://web.archive.org/web/20210405090328/https://www.fda.gov/media/136798/download

On August 23, 2020, FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions. However, adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials. The ongoing clinical trials of investigational convalescent plasma should not be amended based on the issuance of the EUA; health care providers are encouraged to enroll patients in those trials.
….

III. RECOMMENDATIONS

A. Pathways for Use of Investigational Convalescent Plasma

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA, 5 it is regulated as an investigational product. As such, its administration must be under the EUA or an IND. The emergency use of COVID-19 convalescent plasma is not authorized under the EUA unless it is consistent with, and does not exceed, the terms of the Letter of Authorization, including the Scope of Authorization and Conditions of Authorization. 6 Alternatively, investigational convalescent plasma may be administered under the traditional IND regulatory pathway, a single-patient IND for emergency use, or an intermediate-size population expanded access IND (section 351(a)(3) of the PHS Act (42 U.S.C. 262(a)(3)); section 505(i) of the FD&C Act (21 U.S.C. 355(i)); 21 CFR 601.21; and 21 CFR Part 312).

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[3] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx).
[4] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) (Mar. 13, 2020), available at https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-nationalemergency-concerning-novel-coronavirus-disease-covid-19-outbreak/ .
[5] Convalescent plasma is a biological product subject to the licensure requirement under section 351 of the PHS Act. 42 U.S.C. 262(a). 6 See https://www.fda.gov/media/141477/download.....

FDA does not collect convalescent plasma or provide convalescent plasma. Health care providers or acute care facilities should obtain convalescent plasma from an FDAregistered or licensed blood establishment.
The following pathways are available for administering or studying the use of convalescent plasma:

1. Emergency Use Authorization

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On August 23, 2020, FDA issued an EUA for COVID-19 Convalescent Plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions.

Health care providers intending to administer COVID-19 convalescent plasma under the EUA are not required to report its use to FDA. Providers should refer to the Fact Sheet for Health Care Providers7 for information on the intended use and known and potential risks and benefits of COVID-19 convalescent plasma. The Fact Sheet also provides a description of the product, information on the dosage, administration and storage of COVID-19 convalescent plasma, use in specific populations, and instructions for communicating with recipients.

As described in the Fact Sheet, health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of COVID-19 convalescent plasma, and must report fatalities to FDA as required in 21 CFR 606.170. Refer to FDA's guidance entitled "Notifying FDA of Fatalities Related to Blood Collection or Transfusion" for recommendations on reporting fatalities related to blood transfusion to FDA (Ref. 8).

2. Clinical Trials

The EUA is not intended to replace clinical trials that are critically important for the definitive demonstration of safety and efficacy of investigational convalescent plasma. Ongoing clinical trials of investigational convalescent plasma should not be amended based on the issuance of the EUA. Health care providers are encouraged to enroll patients in those trials and complete clinical trials to fully answer the questions about the effectiveness of convalescent plasma for the treatment of COVID-19.

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). The Center for Biologics Evaluation and Research (CBER) Office of Blood Research and Review (OBRR) is committed to engaging with sponsors and reviewing such requests expeditiously. During the COVID-19 pandemic, INDs may be submitted via email to CBERDCC_eMailSub@fda.hhs.gov.

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[7] See https://www.fda.gov/media/141478/download.

Contains Nonbinding Recommendations

3. Expanded Access

An IND application for expanded access is an alternative for use of investigational convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CFR 312.305). During the COVID-19 pandemic, INDs for expanded access, that are not single patient INDs, may be submitted via email to CBERDCC_eMailSub@fda.hhs.gov.

a. Single Patient IND for Emergency Use

Given the public health emergency that the COVID-19 pandemic presents, FDA is continuing to facilitate access to investigational convalescent plasma through the process of a physician requesting a single patient IND for an individual

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patient with serious or life-threatening COVID-19 under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met. Note, in such cases, a licensed physician seeking to administer investigational convalescent plasma to an individual patient must request the IND (21 CFR 312.310(b)).

Note: Given that the intended use of COVID-19 convalescent plasma under the EUA is for treatment of hospitalized COVID-19 patients, FDA expects few requests for single patient INDs. FDA recommends that physicians seeking to use convalescent plasma for hospitalized COVID-19 patients should do so under the EUA and not under single patient INDs. Other options for the use of investigational convalescent plasma are listed above.

To obtain a single patient IND for emergency use, the requesting physician may contact FDA by completing **Form FDA 3926** (https://www.fda.gov/media/98616/download) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov . CBER requests that all forms be filled out electronically to facilitate rapid review. Handwritten forms are often hard to read and may delay the processing of the request. For more detailed instructions see the Form FDA 3926 Instructions (https://www.fda.gov/media/98627/download).

For requests when the provider is unable to complete and submit **Form FDA 3926** due to extenuating circumstances, or in the case of a medical emergency between the hours of 8pm and 8am Eastern Time (ET), i.e., when authorization and issuance of an IND number is needed before 8am ET the next morning, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374 to be routed to the appropriate clinical review staff for assistance with submitting the request and issuance of an IND number. ….

760) 2021-02-12 Karamyan VT: Between two storms, vasoactive peptides or bradykinin underlie severity of COVID-19? The Physiological Society, Physiological Reports REVIEW. 09 March 2021;9 (5):e14796, 1-9. https://physoc.onlinelibrary.wiley.com/doi/10.14814/phy2.14796

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a world-wide pandemic with overwhelming socioeconomic impact. Since inflammation is one of the major causes of COVID-19 complications, the associated molecular mechanisms have been the focus of many studies to better understand this disease and develop improved treatments for patients contracting SARS-CoV-2. Among these, strong emphasis has been placed on pro-inflammatory cytokines, associating severity of COVID-19 with so-called "cytokine storm." More recently, peptide bradykinin, its dysregulated signaling or "bradykinin storm," has emerged as a primary mechanism to explain COVID-19-related complications. Unfortunately, this important development may not fully capture the main molecular players that underlie the disease severity. To this end, in this focused review, several lines of evidence are provided to suggest that in addition to bradykinin, two closely related vasoactive peptides, substance P and neurotensin, are also likely to drive microvascular

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permeability and inflammation, and be responsible for development of COVID-19 pathology. Furthermore, based on published experimental observations, it is postulated that in addition to ACE and neprilysin, peptidase neurolysin (Nln) is also likely to contribute to accumulation of bradykinin, substance P and neurotensin, and progression of the disease. In conclusion, it is proposed that "vasoactive peptide storm" may underlie severity of COVID-19 and that simultaneous inhibition of all three peptidergic systems could be therapeutically more advantageous rather than modulation of any single mechanism alone.

761) 2021-01-13 Fandos N: Trump acquitted of inciting insurrection, Even as bipartisan majority votes 'Guilty'. The New York Times https://www.nytimes.com/2021/02/13/us/politics/trump-impeachment.html

762) 2021-02-13 McConnell M: Mitch McConnell Speech Transcript after vote to acquit Trump in 2nd impeachment trial. Rev https://www.rev.com/blog/transcripts/mitch-mcconnell-speech-transcript-after-vote-to-acquit-trump-in-2nd-impeachment-trial

Mitch McConnell: (00:00)
Mr President.

Speaker 2: (00:01)
The Republican leader.

Mitch McConnell: (00:04)
January 6th was a disgrace. American citizens attacked their own government. They use terrorism to try to stop a specific piece of domestic business they did not like. Fellow Americans beat and bloodied our own police. They stormed the center floor. They tried to hunt down the Speaker of the House. They built a gallows and chatted about murdering the vice president. They did this because they'd been fed wild, falsehoods by the most powerful man on earth because he was angry. He lost an election. Former President Trump's actions preceded the riot or a disgraceful dereliction of duty. The House accused the former president of quote "Incitement". That is a specific term from the criminal law. Let me just put that aside for a moment and reiterate something I said weeks ago. There's no question, none, that President Trump is practically and morally responsible for provoking the events of the day. No question about it.

Mitch McConnell: (01:46)
The people who stormed this building believed they were acting on the wishes and instructions of their president and having that belief was a foreseeable consequence of the growing crescendo of false statements, conspiracy theories, and reckless hyperbole, which the defeated president kept shouting into the largest megaphone on planet Earth. The issue is not only the president in temperate language on January 6th. It is not just his endorsement of remarks in which an associate urged quote "Trial by combat". It was also the entire manufactured atmosphere of looming catastrophe. The increasingly wild myths about a reverse landslide election that was somehow being stolen. Some secret coup by our now president.

Mitch McConnell: (03:09)
Now I defended the president's right to bring any complaints to our legal system. The legal system spoke, the electoral college spoke. As I stood up and said, clearly at that time, the election was settled. It was over, but that just really opened a new chapter of even wilder and more unfounded claims. The leader of the free world cannot spend weeks thundering that

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shadowy forces are stealing our country and then feign surprise when people believe him and do reckless things. I sadly many politicians sometimes make overheated comments or use metaphors. We saw that. That unhinged listeners might take literally, but that was different. That's different from what we saw. This was an intensifying crescendo of conspiracy theories orchestrated by an outgoing president who seemed determined to either overturn the voter's decision or else torch our institutions on the way out. The unconscionable behavior did not end when the violence actually began.

Mitch McConnell: (04:47)
Whatever our ex president claims he thought might happen a day, whatever right reaction he's says he meant to produce by that afternoon we know he was watching the same live television as the rest of us. A mob was assaulting the Capitol in his name, these criminals who are carrying his banners, hanging his flags and screaming their loyalty to him. It was obvious that only President Trump could end this. He was the only one who could. Former aides publicly begged him to do so. Loyal allies frantically called the administration. The president did not act swiftly. He did not do his job. He didn't take steps so federal law could be faithfully executed and order restored. No, instead, according to public reports, he watched television happily as the chaos unfolded. He kept pressing his scheme to overturn the election. Now, even after it was clear to any reasonable observer that Vice President Pence was in serious danger. Even as the mob carrying Trump banners was beating cops and breaching perimeters their president sent a further tweet, attacking his own vice president.

Mitch McConnell: (07:07)
Now predictably and foreseeably under the circumstances, members of the mob seemed to interpret this as a further inspiration to lawlessness and violence not surprisingly. Later, even when the president did halfheartedly began calling for peace he didn't call right away for the riot to end. He did not tell the mob to depart until even later. And even then with police officers bleeding and broken glass covering Capitol floors, he kept repeating election laws and praising the criminals. In recent weeks, our ex-president's associates have tried to use the 74 million Americans who voted to reelect him as a kind of human shield against criticism. Using the 74 million who voted for him as kind of a human seal shield against criticism. Anyone who decries his awful behavior is accused of insulting millions of voters. That's an absurd deflection. 74 million Americans did not invade the Capitol, hundreds of rioters did. 74 million Americans did not engineer the campaign of disinformation and rage that provoked it. One person did, just one.

Mitch McConnell: (09:13)
I've made my view of this episode very plain, but our system of government gave the Senate a specific task. The Constitution gives us a particular role. This body is not invited to act as the nation's overarching moral tribunal. We're not free to work backward from whether the accused party might personally deserve some kind of punishment. Justice Joseph Story, our nations first great constitutional scholar, as he explained nearly 200 years ago, the process of impeachment and conviction is a narrow tool. A narrow tool for a narrow purpose. Story explained this limited tool exists to quote, "Secure the state against gross official misdemeanors", end quote. That is to protect the country from government officers. If President Trump were still in office, I would have carefully considered whether the House managers proved their specific charge. By the strict criminal standard the president's speech probably was not incitement.

Mitch McConnell: (10:58)
However, in the context of impeachment, the Senate might have decided this was acceptable shorthand for the reckless actions that preceded the riot. But in this case, the question is moot because former President Trump is constitutionally not eligible for conviction. Now

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this is a close question. No doubt. Donald Trump was the president when the House voted. Though, not when the House chose to deliver the paper. Brilliant scholars argue both sides of this jurisdictional question. The text is legitimately ambiguous. I respect my colleagues who've reached either conclusion. But after intense reflection, I believe the best constitutional reading shows that article two, section four, exhausts the set of persons who can legitimately be impeached, tried, or convicted. It's the president, it's the vice-president and civil officers. We have no power to convict and disqualify a former office holder who is now a private citizen.

Mitch McConnell: (12:42)
Here is article two, section four, quote, "The president, the vice-president and all civil officers of the United States shall be removed from office on impeachment for and conviction of treason, bribery, or other high crimes and misdemeanors," end quote. Now, everyone basically agrees that the second half of that sentence exhausts the legitimate grounds for conviction. The debates around the Constitution's framing make that abundantly clear. Congress cannot convict for reasons besides those. It therefore follows that the list of persons in that same sentence is also exhausted. There's no reason why one list would be exhaustive, but the other would not. Article two, section four must limit both why impeachment and conviction can occur and to whom if this revision does not limit impeachment and conviction powers then it has no limits at all. The House has sole power of impeachment and the Senate's sole power to try all impeachments, would create an unlimited circular logic empowering Congress to ban any private citizen from federal office.

Mitch McConnell: (14:25)
Now, that's an incredible claim, but it's the argument of the House managers seem to be making. One manager said the House and Senate have quote, "Absolute unqualified, jurisdictional power", end quote. Well, that was very honest because there is no limiting principle in the constitutional text that would empower the Senate to convict former officers that would not also let them convict and disqualify any private citizen, an absurd end result to which no one subscribes. Article two section four must have force. It tells us the president, the vice president, and civil officers may be impeached and convicted. Donald Trump's no longer the president. Likewise, the provision states that officers subject to impeachment and conviction shall be removed from office if convicted. Shall be removed from office, if convicted. As Justice Story explained, the Senate upon conviction is bound, in all cases, to enter a judgment of removal from office. Removal is mandatory upon conviction.

Mitch McConnell: (16:01)
Clearly he explained that mandatory sentence cannot be applied to someone who's left office. The entire process revolves around removal. If removal becomes impossible, conviction becomes insensible. In one light it certainly does seem counterintuitive that an office holder can elude Senate conviction by resignation or exploration of term, an argument we heard made by the managers. But this underscores that impeachment was never meant to be the final forum for American justice. Never meant to be the final forum for American justice. Impeachment conviction and removal are a specific intra-governmental safety valve. It is not the criminal justice system where individual accountability is the paramount goal. Indeed Justice Story specifically reminded that while former officials were not eligible for impeachment or conviction, they were, and this was extremely important, still labile to be tried and punished in the ordinary tribunals of justice. Put another way in the language of today, President Trump is still liable for everything he did while he was in office as an ordinary citizen. Unless the statute of limitations is run, still liable for everything he did while he was in office.

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> Mitch McConnell: (18:04)
> Didn't get away with anything, yet. Yet. We have a criminal justice system in this country. We have civil litigation and former presidents are not immune from being accountable by either one. I believe the Senate was right not to grab power the Constitution doesn't give us. And the Senate was right not to entertain some light speed sham process to try to outrun the loss of jurisdiction. It took both sides more than a week just to produce their pre-trial briefs. Speaker Pelosi's own scheduling decisions conceded what President Biden publicly confirmed, a Senate verdict before inauguration day was never possible. Now, Mr. President this has been a dispiriting time, but the Senate had done our duty. The framers' firewall helped held up again. Oh, in January the sixth, we returned to our posts and certified the election. We were uncowed. We were not intimidated. We finished the job. And since then we resisted the climber to defy our own constitutional guardrails in hot pursuit of a particular outcome.
>
> Mitch McConnell: (19:48)
> We refused to continue a cycle of recklessness by straining our own constitutional boundaries in response. The Senate's decision today does not condone anything that happened on or before that terrible day. It simply shows that senators did what the former president failed to do. We put our constitutional duty first.

763) 2021-02-16 Wosinska M, Zavodszky A, Romine M, McClellan M: Promising practices for promoting utilization of COVID-19 monoclonal antibody treatments. Duke Margolis Center for Health Policy, February 16, 2021. https://healthpolicy.duke.edu/sites/default/files/2021-02/Promising%20Practices%20for%20Promoting%20Utilization%20of%20COVID-19%20Monoclonal%20Antibody%20Treatmentsv4.pdf

764) 2021-02-16. Malani PN, Golub RM: Neutralizing monoclonal antibody for mild to moderate COVID-19. JAMA February 16, 2021; 325(7): 644-645. https://jamanetwork.com/journals/jama/fullarticle/2775645

765) 2021-02-16 Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocheria B, Stosor V, Shawa I, Kumar P, Adams AC, van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM: Effect of Bamlanivimab as monotherapy or in combination with Estevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA 2021 Feb 16; 325 (7): 632-644. file:///Users/andrusmd/Downloads/jama_gottlieb_2021_oi_210002_1613412631.85755%20(2).pdf

> **MAIN OUTCOMES AND MEASURES** The primary end point was change in SARS-CoV-2 log viral load at day 11 (±4 days). Nine prespecified secondary outcome measures were evaluated with comparisons between each treatment group and placebo, and included 3 other measures of viral load, 5 on symptoms, and 1 measure of clinical outcome (the proportion of patients with a COVID-19–related hospitalization, an emergency department [ED] visit, or death at day 29).
>
> **RESULTS** Among the 577 patients who were randomized and received an infusion (mean age, 44.7 [SD, 15.7] years; 315 [54.6%] women), 533 (92.4%) completed the efficacy evaluation period (day 29). The change in log viral load from baseline at day 11 was –3.72 for 700 mg, –4.08

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

for 2800 mg, –3.49 for7000mg,–4.37 for combination treatment, and–3.80 for placebo.Compared with placebo, the differences in the change in log viral load at day 11were0.09 (95% CI, –0.35 to0.52;P = .69) for 700 mg, –0.27 (95% CI, –0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, –0.13 to 0.76; P = .16) for 7000 mg, and –0.57 (95% CI, –1.00 to –0.14; P = .01) for combination treatment. Among the secondary outcome measures, differences between each treatment group vs the placebo group were statistically significant for 10of84endpoints.TheproportionofpatientswithCOVID-19–related hospitalizationsorEDvisitswas5.8% (9events) for placebo, 1.0% (1event) for700mg, 1.9% (2events) for 2800 mg, 2.0% (2 events) for 7000 mg, and 0.9% (1 event) for combination treatment. Immediate hypersensitivity reactions were reported in 9 patients (6 bamlanivimab, 2 combination treatment, and 1 placebo). No deaths occurred during the study treatment.

CONCLUSIONS AND RELEVANCE Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy. Further ongoing clinical trials will focus on assessing the clinical benefit of antispike neutralizing antibodies in patients with COVID-19 as a primary end point.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04427501

766) 2021-02-16 U.S. Food & Drug Administration: Clinical Memorandum. COVID-19 Convalescent Plasma EUA Decision Memo. https://www.fda.gov/media/141480/download is the baseline URL which when placed in the Wayback Machine, 8-23-2020 to 2-2021 is the renewed new memo on CCP EUA issued 2-2021 to the present: https://web.archive.org/web/20210330024720/https://www.fda.gov/media/141480/download

EXECUTIVE SUMMARY

COVID-19 Convalescent Plasma (CCP) was granted Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 on August 23, 2020. At that time, the totality of the scientific evidence supported a determination that the use of CCP in hospitalized patients with COVID-19 met the "may be effective" standard for issuance of an EUA, and it was reasonable to consider that the known and potential benefits of CCP outweighed the known and potential risks for the authorized use.

Following the EUA, emerging evidence from randomized controlled trials has continued to inform this assessment. The available evidence indicates that 1) the use of low titer CCP in hospitalized patients no longer meets the evidentiary standard of "may be effective", and **2) high titer CCP has not demonstrated benefit when administered late in the disease course** in immunocompetent hospitalized patients.

Additional data from RCTs and observational studies support a determination that high titer CCP may be effective when administered **early in the course of illness, particularly prior to the expected time of host antibody response.** In patients with impaired humoral immunity, the potential therapeutic window may be prolonged. As RCT data continue to demonstrate that the risks of CCP do not exceed those observed with plasma transfusion in general, it is reasonable to believe that the known and potential benefits of use of high titer CCP outweigh the known and potential risks when used for the treatment of hospitalized patients with COVID-19, particularly early in the course of illness or in patients with impaired humoral immunity. Results from ongoing RCTs are expected to continue inform the optimal patient populations and product characteristics for efficacy of CCP in COVID-19.

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Recommendation: The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 **early in the course of hospitalization**. The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product characteristics meeting EUA criteria

……

Antibody responses in COVID-19 and timing of CCP transfusion

The relative roles of humoral and cellular immunity in SARS-CoV-2 infection continue to be unraveled, and it appears likely that CD4+ T cells, CD8+ T cells, and neutralizing antibody responses all contribute to control of SARS-CoV-2 infection in both non-hospitalized and hospitalized cases of COVID-19[23]. The large majority of patients with SARS-CoV-2 infection will seroconvert within 5-15 days post-symptom onset, with 90% seroconverting by day 10[23-25]. IgM and IgG antibodies are frequently detected concurrently[26], and peak anti-spike or anti-RBD IgG levels are reached by approximately 15 days post symptom onset[27]. Antibody responses and memory B cells appear to persist for at least 5 months and antibodies may be a correlate of immune protection[28-31]. Delayed antibody response kinetics also appear to be associated with more severe disease[27, 32]. At the same time, studies have generally shown higher titers in patients following recovery from severe disease compared to mild or asymptomatic illness[25, 33].

The observation that high titer CCP was beneficial when administered within 72 hours of symptom onset in high risk subjects, but failed to demonstrate benefit in trials where the median duration of symptoms was 8 days or longer, indicates benefit with CCP transfusion is more likely in patients early in the humoral immune response when host antibody titers remain undetectable or low (i.e., likely within the first week following symptom onset). This is consistent with longstanding historical precedent in passive immune therapies for viral infections, where prophylactic or early use has generally been more effective than in established infections[34].

These trends are also consistent with clinical evidence for administration of anti-SARS-CoV-2 monoclonal antibodies, where benefit has been demonstrated with early outpatient use, but not in hospitalized patients within 12 days of symptom onset[35-37] as described in the following two studies:

In outpatient studies of bamlanivimab in recently diagnosed patients with mild to moderate disease (BLAZE-1)[36], subjects were excluded if they were previously known to be seropositive. Subjects had a median of 4 days of symptoms at the time of infusion, and the study found one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time. While reduction in viral load was the primary endpoint in this phase 2 trial, subjects treated with bamlanivimab also showed a nominally statistically significant reduction in COVID-19 related hospitalizations or ED visits within 28 days in the pooled dose-level data.

In outpatient studies of casirivimab/imdevimab in symptomatic patients with mild to moderate COVID-19 (R10933-10987-COV-2067), subjects who were no more than 7 days from symptom enrollment were included regardless of serostatus[35]. Casirivimab/imdevimab treatment reduced viral load, and patients who were seronegative at baseline showed larger reductions in

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viral load and a larger reduction in the proportion of subjects with at least one medically attended visit compared to the overall population. Based on these studies, both therapies were granted EUA for use in high risk outpatients with mild to moderate COVID-19 (https://www.fda.gov/media/143892/download, https://www.fda.gov/media/143603/download).

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In early studies of the COVID-19 pandemic, the median time from symptom onset to the development of dyspnea was approximately 5-8 days[38, 39], and patients who develop critical illness typically do so shortly thereafter (days 8-10)[40]. While the study by Libster et al[10] demonstrated a reduction in progression to severe disease in high risk outpatients within 72 hours of the onset of symptoms, one factor complicating very early use of CCP in the outpatient population is the evidence that a large proportion of these patients will have a self-limited illness and will not go on to severe or critical illness even without targeted intervention[41]. Therefore, in the early-disease outpatient population, it is important to have a full understanding of the relative benefit and identify high-risk populations so that the known and potential risks of transfusion are outweighed by the known and potential benefits of CCP. Ongoing randomized controlled trials will be critical to determine the clinical and laboratory parameters that can identify where the potential benefit of CCP outweighs the potential risk in outpatients.

Based on the study by Libster et al[10] the therapeutic window appears to be at least within 72 hours of symptom onset, while additional negative RCTs with a median duration of symptoms prior to transfusion of 8 days indicating that 8 days after symptom onset may be too late for efficacy of CCP in immunocompetent hospitalized COVID-19 patients. These timepoints appear to correlate with the timing of the patients' own antibody responses to infection, such that by the time a patient is forming their own antibodies, benefit from CCP appears unlikely. The time period between 3 and 7 days remains to be studied rigorously in randomized trials of CCP, but observational studies, preclinical studies, studies of related therapies, and what is known about the timing of the adaptive immune response in SARS-CoV-2 infection suggest that high titer CCP may be effective in this window period. As noted above, this window appears to be longer in the setting of impaired or deficient humoral immunity. Nonetheless, adequate and well controlled trials in this time period remain necessary for a conclusive demonstration of efficacy.

767) 2021-02-16 Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Most recent update. http://web.archive.org/web/20210408021730/https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

768) 2021-02-17 Wilt TJ, Kaka AS, MacDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults – A Living Review. Updated February 2021, Health Services Research & Development Service, U.S. Department of Veterans Affairs. https://web.archive.org/web/20210319093451/https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.cfm

769) 2021-02-17 Sauber R: Letter to Michael R. Hogan, Designated Agency Ethics Official…In a letter of February 17, 2021. https://extapps2.oge.gov/201/Presiden.nsf/PAS+Index/249BEDEAC38845E48525868D0032DC51/$FILE/Sauber,%20Richard%20%20finalEA.pdf

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770) 2021-02-18 Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published on January 13, 2021) This editorial was republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 – 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678 In the article, it was not disclosed that Dr. Katz is the Chief Medical Director, ImpactLife: https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/

[Please note that Dr. Katz was not fully identified by this paper. Dr. Katz is "…the former Chief Medical Officer at **A**merica's **B**lood **C**enters in Washington, DC, an ABC past president, former board member and a past chair of its Scientific, Medical and Technical Committee. His transfusion medicine career has been dominated by attention to transfusion transmitted infections. He has served multiple terms as the chair of the AABB Transfusion Transmitted Diseases committee and served on many AABB committee and working groups. Dr. Katz is on the Editorial Board of the journal Transfusion, has served on the FDA Blood Products Advisory Committee as a member, industry representative and chair, and is a current member of the HHS Advisory Committee on Blood and Tissue Safety and Availability." – Winn KI, Katz L, Goel R: Dr. Louis Katz, Acting Chief Medical Director. ImpactLife (formerly Mississippi Valley Regional Blood Center). https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/]

The text of this article that follows is verbatim because it explains the mindset of those involved in the FDA's, NIH's, and The White House's convoluted obfuscation in the lack of treatment during the viremic phase of those infected with COVID-19 with passive immunization (Covid-19 Convalescent Plasma [CCP]) ***AND THE COVER-UP by US Medicine and the US Government THAT HAS BEEN PERVASIVE OVER THE LAST 15 months.*** *While advocating for the appropriate administration early in the viremic phase of Covid-19 (<72 hours from symptoms/diagnosis) in the outpatient setting and NOT IN THE HOSPITAL SETTING, this New England Journal of Medicine editorial fails strongly to emphasis the definitive utility of PASSIVE IMMUNIZATION and thus has been ignored by the medical community, the US federal government, and the US public-at-large.* ***Even after the FDA quietly removed from all its official documentation on 9/2/2020 mandating the strict erroneous CCP administration critera initiated by the FDA / vis-à-vis The White House on March 24, 2020 for use only in severely affected patients--late in the disease--administration of CCP (during the cytokine cascade and bradykinin phase which both are dominant in severely hospitalized patients and then only somewhat effective treatment is supportive) continued. The wrong-time administration of CCP became the de facto standard-of-care. The majority of 722,000 doses of CCP given over the last 15 months to individuals late in their disease course throughout the U.S.A. (and much of the World) was given at the WRONG TIME.*** –

And the FDA, the NIH, the VA, *The White House,* the *New England Journal of Medicine, etc.* *knew it!*

PASSIVE IMMUNOTHERAPY has been used since the late 19th century, and in 1901, the first Nobel Prize in Physiology or Medicine was awarded for serum therapy for patients with diphtheria. During the 1918 pandemic, serum from convalescent patients was used to treat influenza, with some apparent success.1 Today, the use of immunoglobulins has been established for the prophylaxis and treatment of a variety of infections, including those with respiratory syncytial virus, cytomegalovirus, and hepatitis B or hepatitis A virus. More recently, passive immunotherapy has been evaluated for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and Ebola virus disease. Intravenous human immunoglobulin has revolutionized the management of immunoglobulin deficiency states.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

The use of convalescent plasma against SARS coronavirus 2 (SARS-CoV-2) is advocated for the treatment of patients with coronavirus disease 2019 (Covid-19). The experience with influenza A is relevant, and a meta-analysis suggested that **early treatment, before critical illness develops**, may be an important **predictor of the efficacy of passive immunotherapy for that pathogen**.1 The authors of that meta-analysis acknowledged the low quality of the available evidence regarding early treatment. Another meta-analysis of studies of convalescent plasma and hyperimmune immunoglobulin in patients with influenza A and SARS suggested a mortality benefit **"when convalescent plasma is administered early after symptom onset."**2 However, in a randomized, controlled trial, high-titer convalescent plasma from patients who had recovered from H1N1 influenza was ineffective against severe influenza A infection in hospitalized children and adults.3

Initial randomized trials of convalescent plasma in patients with Covid-19 focused on hospitalized patients who were already moderately to severely ill, and these trials provided weak evidence of clinical efficacy.[4-6] **Some were underpowered** when nonpharmaceutical interventions such as masking and social and physical distancing reduced the incidence of Covid-19 and enrollment was limited. Also, these trials were heterogeneous with respect to the characteristics of the convalescent plasma used (e.g., its antibody content and the stratification of the recipients according to their serologic status). **No unexpected safety signals beyond the recognized risks of plasma transfusion (i.e., fluid overload, transfusion-associated acute lung injury, and allergy) have emerged, nor has there been evidence of antibody-dependent enhancement of Covid-19 severity**. Accordingly, it is difficult to make actionable conclusions about the clinical value of convalescent plasma.

Observational studies have been more positive than randomized trials; some, but not all, of these studies have suggested modest clinical effects and measurable surrogate virologic outcomes.[7,8] They have confirmed the safety profile of plasma transfusions but have some of the same issues as randomized trials, in addition to the potential biases and shortcomings inherent in observational studies.

The Food and Drug Administration (FDA) argued that a "totality of the evidence" suggested that the benefits of convalescent plasma would outweigh its risks, and given the lack of effective treatments, **the FDA granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma in hospitalized patients with signs of progressive infection.** By contrast, a National Institutes of Health guidelines panel stated that "the data are insufficient to recommend for or against" the use of convalescent plasma. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommend that the use of convalescent plasma be limited to clinical trials, that critically ill patients and **those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma**, and **that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes.**9

Considering the number of SARS-CoV-2 infections, the paucity of treatment options, and the enthusiasm for and controversy about convalescent plasma, a high-quality, multicenter, randomized, controlled trial is most welcome. **Libster and colleagues now report in the *Journal*[10] the results of a well-executed trial of early convalescent plasma in older adult patients in whom symptomatic SARS-CoV-2 infection was diagnosed with the use of a polymerase-chain-reaction assay. In this double-blind trial, 250 ml of convalescent plasma with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein was compared with saline placebo in patients who were 65 to 74 years of age and had prespecified**

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coexisting conditions and in patients who were 75 years of age or older with or without coexisting conditions.

The patients received convalescent plasma or placebo less than 72 hours after symptom onset. In the intention-to-treat population, a primary end-point event (progression to predefined severe disease during follow-up) occurred in 16% (13 of 80 patients) and 31% (25 of 80 patients) of the well-matched convalescent plasma and placebo groups, respectively. A dose-dependent effect relative to the antibody titers after infusion was observed, and this effect was larger after the exclusion of 6 patients who had a primary end-point event before infusion. The benefits of convalescent plasma with respect to the secondary end points were consistent with those associated with the primary end point. No serious adverse events were observed. **The authors conclude that "early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19."** Even before the current trial, **the EUA emphasized the potential advantages of early therapy with high-titer convalescent plasma.** Unfortunately, a direct comparison of antibody levels in the current trial with assays specified in the FDA EUA is not available. Antibody titers in the recipients at enrollment were not provided, so no comment can be made about the usefulness of seroreactivity in patients as a criterion for convalescent plasma use.

At this time, convalescent plasma should be reserved for patients in whom the duration, severity, and risk of progression of illness are similar to those in the patients in this trial. Younger high-risk patients (and certain immunodeficient patients) with these disease characteristics should be considered as well.

The supply of convalescent plasma has been tenuous during the marked increase in Covid-19 cases during the fall in the United States, although recent collections have improved. From September 28 through December 27, 2020, distributions of new and stockpiled units of convalescent plasma to hospitals in the United States exceeded collections by 7785 units (Block W: personal communication). **If collections are restricted to the high-antibody titers and patient indications described in the article by Libster et al., the supply of convalescent plasma will be stressed. At my center, high-titer collections (as defined by the FDA) account for only 19.5% of seroreactive convalescent plasma donations. Shifting the pool of potential recipients away from those included in the EUA to the many infected outpatients whose risk of hospitalization and eventual need for advanced care cannot be precisely estimated should lead to the extension of convalescent plasma transfusions to prehospital venues (although this is not yet permitted in the EUA).**

Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be discouraged, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU. Constraints on therapies for Covid-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines.

In an obfuscating way, Dr. Katz confirms that when high-dose COVID-19 Convalescent Plasma is given **EARLY**(<72 from time of onset or diagnosis) and is compared with placebo in age-matched patients ~70 years of age, progression to severe COVID-19 disease (e.g. pneumonitis, blood clots, etc.) is 16% versus 31%, respectively.

THUS, COVID-19 CONVALESCENT PLASMA when given ***EARLY to an AGE COHESIVE GROUP*** in the VIREMIC PHASE OF COVID-19 (<72 HOURS) has a 50% DECREASED / OBSERVED REDUCTION IN PROGRESSION to the LATER MULTIORGAN-SYSTEM PHASE

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

OF COVID-19 INVOLVING (1) THE CYTOKINE CASCADE STORM and (2) the ACCUMULATION OF DETRIMENTAL LEVELS OF BRADYKININ.

771) 2021-02-18 Whyte J: FDA revises EUA for COVID-19 Convalescent Plasma. WebMD. John Whyte, M.D., Chief Medical Officer at WebMD interviews Peter Marks, M.D., PhD, Director for the Center for Biologics Evaluation and Research at the U.S. FDA: FDA revises EUA for COVID-19 convalescent plasma. https://www.webmd.com/coronavirus-in-context/video/peter-marks-plasma

The following is a very important interview as Peter Marks, M.D., PhD as the Director for CBER at the FDA had the ability in March 2020 to have designated COVID-19 Convalescent Plasma a Biosimilar Biologic (like rabies vaccine, HyperTet, RhoGam, IVIG, etc.) and the designation of "Investigational" and all the Expanded Access / (compassionate use only) would have been avoided. This would have precluded the issuing of the eligibility criteria of March 24, 2020 which directed administration late in the course of the disease—THE WRONG TIME as is confirmed by Dr. Marks in the 2/18/2021 interview! Immediately following is from the March 24, 2021 FDA announcement. https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

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- **Eligible patients for use under expanded access provisions:**
  - Must have laboratory confirmed COVID-19
  - Must have severe or immediately life-threatening COVID-19, for example:[1]
    - Severe disease is defined as:
      - dyspnea,
      - respiratory frequency ≥ 30/min,
      - blood oxygen saturation ≤ 93%,
      - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
      - lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening disease is defined as:
      - respiratory failure,
      - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/3

27/3/2020 Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

      - multiple organ dysfunction or failure
  - Must provide informed consent

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

[1]Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Start of the interview of Dr. Marks by Dr. Whyte:

> JOHN WHYTE: Welcome, everyone. You're watching "Coronavirus in Context." I'm Dr. John Whyte, chief medical officer at WebMD. We're spending a lot of time talking about vaccines. But we can't forget about the role of therapeutics for those persons who have caught COVID and are having a serious case. And there's been some recent changes in when and how we should use convalescent plasma.
>
> So to help explain these changes, I've asked Dr. Peter Marks. He's the director for the Center for Biologics Evaluation and Research at the US Food and Drug Administration. Welcome back, Dr. Marks.

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PETER MARKS: Thanks very much for having me.

JOHN WHYTE: Let's just take a minute and remind our audience-- we have a lot of folks from Medscape, but also consumers-- what is convalescent plasma?

PETER MARKS: So convalescent plasma is the blood plasma that's taken from an individual who has been infected with COVID-19 and who's recovered from the infection. In some cases, they might not even have known they had the infection, but they obviously did. And they might have antibodies that have been detected and told they had COVID-19, or they might have had a PCR test when they were sick with COVID, were told they had COVID-19, and afterwards, after they recover and they're fully recovered, they're eligible to potentially donate convalescent plasma, which is usually taken by plasmapheresis. People are put on a machine for about an hour, and the blood products taken out. And the blood cells are given back to the person. The plasma is taken off.

JOHN WHYTE: Now, the FDA authorized the use, under an emergency use authorization, of convalescent plasma in August of last year. And recently, you revised that authorization-- actually, in many ways made it more restrictive. Let's go over what the change in the EUA is.

PETER MARKS: Right. So the emergency use authorization that was issued in August was a very broad emergency use authorization, because at that time we were relying on the evidence at the time which said that it appeared that convalescent plasma could potentially benefit a broad swath of people. And we weren't really sure who it might benefit the absolute most. We knew it was best when given in high titer, and we knew that it seemed to be best in people who were treated earlier. But we couldn't rule out that it was having some benefit to people later on in the course of disease.

JOHN WHYTE: And at that time, they didn't have to be hospitalized.

PETER MARKS: We always required that the patients be hospitalized. It was always hospitalized patients. And what happened, then, is over the course of the past few months-- we follow the literature very closely-- there have been studies that have come out of various places. Some have been negative for convalescent plasma-- they said that it's not had a beneficial effect. Others have been quite positive.

And over the course of time, we've looked closely at them, and we sorted them out. And it became pretty clear that when people were treated early on with high-titer convalescent plasma, they seemed to be showing some benefit. And when you treat late, you just don't see that benefit. Particularly when you treat people who have been on a ventilator, it just-- with the rare exception of people who have defects in immunity, people who have diseases like hematologic malignancies like chronic lymphocytic leukemia-- those people, they may benefit late on, because they don't make antibodies.

But for the large majority of people who have normal immune systems, if you treat late, convalescent plasma is not seeming to benefit, whereas if you treat early, within the first few days after diagnosis, the data are increasingly supporting that there is some benefit there. It's not a massive benefit. It's a modest benefit.

JOHN WHYTE: How would you articulate that benefit?

PETER MARKS: I can cite the data that we have from roughly 20,000 individuals who received 1 unit of convalescent plasma. Roughly half of those people got high titer and half of them got low titer of various levels. And the people who got the higher-titer plasma had about a 2-percent absolute reduction in mortality at seven days, which translates into about a 15-percent relative reduction if they were not intubated.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

If they were intubated, they were on a ventilator, then there really wasn't any benefit. So those data really helped push us along towards saying it was time to kind of narrow down the emergency use authorization to say, look, don't use this late in people who are intubated-- that is, on a ventilator. Use it early on or earlier on in the course of disease.

Now, your next question might be, why not just use it as an outpatient? Hum. And the answer is--

JOHN WHYTE: Now you're interviewing yourself.

PETER MARKS: Nah. I might as well do that. I've done this enough. But the reason why we're not there yet is because we're waiting for some very well-designed studies that are being conducted, one by the National Heart, Lung, and Blood Institute, which will give us a good answer about the potential benefit in that setting.

JOHN WHYTE: Well, that's why I was asking you about hospitalized patients. Because if we talk about-- you mentioned it has to be used early on in the disease-- but what about severity of disease? Because many patients that aren't coming to the hospital until they're much further along-- so how do you do it, in the sense you want to do it early on, within those first couple of days, but sometimes we're telling patients not to come to the hospital or to the ER. So how do we balance that? So what's the severity of disease?

PETER MARKS: I think right now the way we balance it is we say that if you're somebody who's got early disease and you're interested, get onto the www.ClinicalTrials.gov and find one of the sites around you that might be doing outpatient clinical trials with convalescent plasma. There are a number of sites doing that.

But I think, otherwise, when people are admitted to the hospital, it's probably a good thing for physicians to think right away, is this somebody for whom convalescent plasma may make sense? Again, if someone's intubated in that first couple days, maybe not. On the other hand, if someone needs supplemental oxygen, those patients did seem to benefit.

JOHN WHYTE: Now, let's talk about the person's underlying immune response, their humoral immunity. So who are those patients? Many patients are often asking about, what if they're immunocompromised? What do they qualify for? Talk to our listeners about what's that patient population-- because that's a component, their underlying immunity function.

PETER MARKS: So it's a great question. And we've actually kept up with the case reports that have been coming out. They're not trials, but they're a case series that have come out from around the globe, and it's very convergent. If you treat people who don't make a sufficient amount of antibody, either because they have a primary immunodeficiency syndrome or because they have [INAUDIBLE] cancer, and they can't make them, if you treat them, even if you seem to treat those people late, they seem to have benefit.

And there are some amazing case reports-- obviously, it's always N-of-1-- case reports, you always have to take with a grain of salt-- but where people even very late on have had very good responses clearing viremia. So that kind of makes sense, right? Because if you're not able-- what we think, at least, that the antibodies are doing here-- the antibodies in convalescent plasma are acting like an antiviral, right? And if you give it early, they're acting like an antiviral would early on in getting things under control. Later on in the course of disease, where there are other organ damage effects, that's not the best time for an antiviral. And for those who are immunocompromised, it may be that they just have ongoing viremia, and you need to clear it. And giving them convalescent plasma helps take care of that.

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JOHN WHYTE: One question we have gotten asked, Dr. Marks, is for those patients who have been fully immunized, are they able to donate plasma?

PETER MARKS: So it's a great question. And it's one we're still debating. Right now, if people have not had COVID-19 and get immunized-- so they're people who are COVID-19-negative to start, then get immunized-- we're not considering them as convalescent plasma donors, because they're making antibodies against just the S protein that are in the current generation of mRNA vaccines that are authorized.

We don't know, in terms of the convalescent plasma response that we're seeing, how much of the benefit is from the S-protein antibodies versus N-protein antibodies or other antibodies that are there. And until we have a little better idea on that, we're a little hesitant to swing over to have vaccinated individuals donate.

But this is an absolutely great question, because we're very much looking into this now. It would be nice to understand, because soon we're going to have a large population of people who will be fully vaccinated, probably with high titers of S antibodies, and it would be nice to know this. So stay tuned. We do that for other infectious diseases, and maybe we'll see it coming for COVID-19 soon enough.

JOHN WHYTE: Tell us how staff are doing. You had your general work that you had to do, in terms of vaccines, other biologics. Now you have the whole issue of COVID. How is everyone managing it?

PETER MARKS: Well, I have to say, we are incredibly lucky at FDA. We have a staff that has risen to the occasion in an amazing way. They're keeping the normal freight moving. And while they're keeping the normal freight moving, they are taking care of the avalanche of COVID-19-related applications.

Now, in some areas, there are a little lower number of applications than in others. But if you look, for instance, in the vaccine area, there is an avalanche there. And they're doing an incredible job keeping up. Same thing with, actually, some of the cellular therapies that have come in, and even the antibody therapies, et cetera. There are lots of them, right?

Our folks have done just an incredible job pitching in. People who have a little less work pitch in to those who are almost getting underwater in work. So it's been really wonderful. It has taken its toll. People are getting a little tired. And we're trying to make sure that we take care of people. But we're very lucky that people have really had such commitment to public health.

JOHN WHYTE: Absolutely. And then finally, all these emergency use authorizations that are happening across the agency-- do you expect sponsors to apply for full licensure in a few months?

PETER MARKS: Yeah. So I-- for the vaccine sponsors in particular, we've told them that if they want to come in for an EUA, they should expect-- it's actually in our guidance-- they should expect that they're going to come in for a biologics license application. And so that's why the work isn't going to end soon, because as we're now dealing with some of the emergency use authorizations where the vaccines are becoming more mature, they've been in use for a little bit, I would suspect in the not-too-distant future we may see their biologics license applications. And so there will be kind of a cohort that will come along of license applications in the coming months.

JOHN WHYTE: Well, Dr. Marks, I want to thank you for taking the time, the work that you and all the staff at the Center for Biologics Evaluation and Research and all of FDA are doing to keep us all safe.

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PETER MARKS: Thanks so much for having me today.

JOHN WHYTE: And if you have any questions about COVID, drop me a line. You can email us at drjohn@webmd.net as well as post it on Facebook, Twitter, and Instagram. Thanks for watching.

772) 2021-02-20 CDC: History of smallpox. https://www.cdc.gov/smallpox/history/history.html

773) 2021-02-23 Casadevall A, Henderson JP, Joyner MJ, Pirofski LA: SARS-CoV-2 variants and convalescent plasma: reality, fallacies, and opportunities. J Clinical Investigation 2021 Feb 23; 131 (7): e148832. https://www.jci.org/articles/view/148832/pdf

774) 2021-02-23 Hinton DM: U.S. Food and Drug Administration Letter to Nikki Bratcher-Bowman, Acting Assistant Secretary for Preparedness and Response, EUA-update regarding COVID-19 Convalescent plasma. February 23, 2021 http://web.archive.org/web/20210302010613/https://www.fda.gov/media/141477/download

775) 2021-02-24 Biden JR: Notice on the Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic. February 24, 2021 – Presidential Actions https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/notice-on-the-continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic/

776) 2021-02-25 Hinton DM: Emergency Use Authorization 094 regarding combination of bamlanivimab and etesevimab. (EUA led to the revocation of EUAs for bamlanivimab only). https://www.fda.gov/media/145801/download

777) 2021-02-25. Munz M: More monoclonal antibody infusion centers open in St. Louis area, helping prevent COVID-related hospitalizations. St. Louis Post-Dispatch. February 25, 2021. https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/more-monoclonal-antibody-infusion-centers-open-in-st-louis-area-helping-prevent-covid-related-hospitalizations/article_5e2461ac-1397-5ddf-89b2-c6fa35710ed1.html

> *When severely ill with COVID-19, a person experiences two phases – an early phase dominated by the virus reproducing itself, which happens a lot in the lungs and leads to low oxygen levels; and a later phase where the body's immune system has a dangerous overreaction to the infection, which causes damage to other organs.*
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> *"The early phase, when the virus is really doing most of its reproduction and a lot damage, that's when we want to interfere with that reproduction. And that's what these antibodies do," said* ***Dr. Bruce Hall****, chief quality officer for BJC HealthCare.*
>
> *That's why it's important to get tested at the first signs of illness and immediately contact a doctor, who must assess and refer patients for the infusion therapy,* ***Hall*** *said.*

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The infusion takes about an hour, and patients are observed for another hour for any adverse reactions, the providers said. The centers are designed so infected patients do not share any space or entrances with other patients, some even requiring their own elevator.

*Monoclonal antibody therapies for COVID-19 made by Eli Lilly and Regeneron were **approved for emergency use by the FDA** in November. To ensure access, the U.S. Department of Health and Human Services purchased over a million doses of the therapies and made them available to states at no cost. Doses are free of charge to patients.*

The treatments have faced barriers to getting started, however, because of the time and logistics involved for the infusions.

Hospitals were swamped with caring for patients during the hardest-hit months of the pandemic and then tasked with setting up vaccinations. Many patients also may not know about the therapies or have the perceptions that they are only available to the well-connected, as they gained publicity when used by former President Donald Trump and other politicians. [e.g.: Trump, Carson, Christy, Giuliani, etc]

*"It takes a little bit of effort to arrange and coordinate and manage the patients appropriately, but we think that it's all worth it if we can keep patients out of the hospital," said **Hall** with BJC, which has infusion centers at Christian Hospital in north St. Louis County, a Missouri Baptist Medical Center Clinic in Sunset Hills, Memorial Hospital in Belleville, Barnes-Jewish Hospital in St. Louis, and Boone Hospital Center in Columbia, Missouri.*

*Studies show that for every 15 people treated, one will be saved from needing to be hospitalized with COVID-19, **Hall** said. So far, the BJC locations are seeing similar results.*

"That's probably a 30 to 40% reduction or more in terms of the risk of having to go into the hospital," he said. "For a disease that can be fatal, we are reducing that need to go into the hospital substantially."

> [*] **Bruce Hall, M.D., Ph.D., F.A.C.S., Professor of Surgery, Washington University School of Medicine (WUSOM). Through the VA-University Affiliation of 1946[**], PL 79-293, both Dr. Hall and I are Attending Surgeons at the St. Louis (John Cochran) VAMC and Professors of Surgery from our respective universities: WUSOM and Saint Louis University School of Medicine (SLUSOM). Our desks are across the hall from each other on 5N of JCVAMC in A558, Unit I [WU] General Surgery and in A555, Unit II [SLU] General Surgery, respectively. Bruce's cell is: 314-401-0247 and my wife, Pam's cell is: 314-809-9634.**
>
> [**] **U.S. Department of Veterans Affairs Research and Development: Milestones in VA-Academic Collaboration, https://www.research.va.gov/researchweek/press_packet/Collaboration.pdf , December 2016.**
>
> https://www.bjc.org//Portals/0/Coronavirus/mAb-algorithm.pdf

BJC Monoclonal Antibody treatment for COVID-19
https://www.bjc.org/Coronavirus/mAb-for-COVID

778) 2021-02-25 BJC: Monoclonal antibody treatment for COVID-19. (first captured on the Way Back Machine 2/25/2021) https://web.archive.org/web/20210225225153/https://www.bjc.org/Coronavirus/mAb-for-COVID-1 (Latest version: https://www.bjc.org/Coronavirus/mAb-for-COVID-1)

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779) 2021-02-26. U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210226104738/https://www.fda.gov/media/141480/download

780) 2021-02-26 Robbins R: The Biden administration buys 100,000 doses of a combination antibody treatment for high-risk Covid-19 patients. The New York Times, Feb 26, 2021. https://www.nytimes.com/2021/02/26/world/bamlanivimab-etesevimab-eli-lilly-monoclonal-antibodies.html

781) 2021-02-28 U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210228162844/https://www.fda.gov/media/141480/download

782) 2021-02-28 NIH-COVID-19 Treatment Guidelines, Convalescent Plasma, *Last Update: October 9, 2020.* February 28, 2021. https://web.archive.org/web/20210228150338/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

[One will note, that even though the FDA had issued several EUAs, most significantly on February 4, 2021, the NIH continued its section on Convalescent Plasma after was based on the August 23, 2020 EUA announced by President Trump. The FDA Inclusion Criteria of only in Severe COVID-19 affected patients existed from March 24, 2020 until September 2, 2020. Most NIH registered prospective ClinicalTrials existing on September 2, 2020 were based on ***That ERRONEOUS Inclusion Criteria.*** *Note that from October 9, 2020 to February 28, 2021, the NIH hedged its bets by including in the Convalescent Plasma last updated October 9, 2020: ..suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.*

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Convalescent Plasma

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.[1]

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.[2,3] Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.[4,5] Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents.[3,6,7]

783) 2021-03-01 van Beusekom M: COVID meta-analysis: No benefit from convalescent plasma. CIDRAP, Center for Infectious Disease Research and Policy, University of Minnesota. https://www.cidrap.umn.edu/news-perspective/2021/03/covid-meta-analysis-no-benefit-convalescent-plasma

784) 2021-03-02 Hinton DM: Emergency Use Authorization 090 regarding Eli Lilly's bamlanivimab, March 2, 2021. (Now stamped REVOKED—revoked 4-16-2021) https://www.fda.gov/media/143602/download

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785) 2021-03-02 NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms – Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms

The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was: https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1
There are no reported results on the ClinicalTrials website of which the NIH is making its decision to halt the trial. The trial was underpowered where there was no stratification by age and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: **SIREN**, **S**trategies to **I**nnovate eme**R**g**EN**cy Care Clinical Trials, https://clic-ctsa.org/node/9426 .

NIH Announcement to discontinue the trial on March 2, 2021:

Launched in August 2020, the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO(link is external)) was being conducted at 47 hospital emergency departments across the United States and had enrolled 511 of the 900 participant recruitment goal. It was specifically looking at the effectiveness of COVID-19 convalescent plasma – blood plasma derived from patients who have recovered from COVID-19 – in adults who came to an emergency department with mild to moderate symptoms they had for a week or less. These patients also had at least one risk factor associated with severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease, but none were ill enough at the time to be hospitalized.

(C3PO(link is external) https://siren.network/clinical-trials/c3po

C3PO Clinical Trial of COVID-19 Convalescent Plasma of Outpatients

Registered with ClinicalTrials.gov: NCT04355767
{
https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1
This is a registered NIH ClinicalTrials.gov
Award Number: 1OT2HL156812-01
Status: No new randomizations as of February 25, 2021.
NIH Press Release (March 2, 2021)

- Media inquiries: Refer to **Lenora Johnson, DrPH, MPH** and **Mark Sampson**, and to this press release.

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The Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) is a multi-center randomized, single blind, two arm, placebo controlled phase III trial with blinded outcome assessment to establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.

COVID-19 is a respiratory illness caused by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). As of May 1, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. The majority (80%) of cases are categorized as mild, while approximately 15-20% of cases are categorized as severe, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure. Among the 5% who develop severe disease, as many as 50% die. At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease.

Passive antibody therapy using plasma from donors who have been infected and then recovered (convalescent plasma, CP) contains neutralizing antibodies against the infectious agent. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic. Use of CP for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. At this moment, there is no high quality evidence to support the efficacy of CP for treating COVID-19 illness. Conceptually, CP has the highest chance of showing efficacy if used for early treatment of patients at the highest risk for severe disease and mortality.

The overarching goal of this trial is to confirm or refute the role of passive immunization as a safe and efficacious therapy in preventing the progression from mild to severe/critical COVID-19 illness and to understand the immunologic kinetics of anti-SARS-CoV-2 antibodies after passive immunization.

For more information on C3PO and convalescent plasma go to our In the News page. (https://siren.network/clinical-trials/c3po/in-the-news)

C3PO IN THE NEWS

March 10, 2021

- Convalescent Plasma Strikes Out As COVID-19 Treatment
  https://www.npr.org/975365309

October 22, 2020

- OHSU reserchers say they're having trouble recruiting patients for COVID-19 convalescent plasma trial
  https://www.kptv.com/ohsu-researchers-say-theyre-having-trouble-recruiting-patients-for-covid-19-convalescent-plasma-trial/video_767f3558-10aa-5201-ad47-94322b60070d.html?block_id=988363

September 8, 2020

- NIH clinical trial explores use of convalescent plasma in at-risk outpatients with early COVID-19
  https://www.nhlbi.nih.gov/news/2020/nih-clinical-trial-explores-use-convalescent-plasma-risk-outpatients-early-covid-19

August 25, 2020

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- UF Health enrolls first patients in national COVID-19 study on convalescent blood plasma

  https://m.ufhealth.org/news/2020/uf-health-enrolls-first-patients-national-covid-19-study-convalescent-blood-plasma

August 19, 2020

- New clinical trial at OHSU tests donated antibodies

  https://news.ohsu.edu/2020/08/18/new-clinical-trial-at-ohsu-tests-donated-antibodies

August 6, 2020

- Will COVID-19 finally provide an answer on convalescent plasma?

  https://www.medpagetoday.com/infectiousdisease/covid19/87936

August 3, 2020

- UM and Other Michigan hospitals to treat COVID-19 patients with convalescent plasm.

  https://www.michiganradio.org/post/um-and-other-michigan-hospitals-treat-covid-19-patients-convalescent-plasma

July 30, 2020

- Michigan hospitals test if plasma from recovering patients can curb COVID-19

  https://www.bridgemi.com/michigan-health-watch/michigan-hospitals-test-if-plasma-recovering-patients-can-curb-covid-19

- Researchers at the University of Michigan's Michigan Medicine and three other medical centers were awarded a total of $7 million from the National Heart, Lung, and Blood Institute (NHBLI) to study convalescent plasma in reducing symptoms of COVID-19 in patients with mild cases, Michigan Medicine announced Thursday.

  https://www.clickondetroit.com/video/health/2020/07/30/michigan-medicine-7-million-in-funding-for-covid-19-therapy-trial/

- Michigan Medicine and three other medical centers receive $7 million COVID-19 outpatient convalescent plasma therapy trial

  https://www.uofmhealth.org/news/archive/202007/michigan-medicine-and-three-other-medical-centers-receive-7?fbclid=IwAR2Rr1QbiOj6OxC0dcbv2Hw0Cn6uMlnx0BTz-buGJCf4SozAqutNDa6_1qo

- Trump urges people who who have recovered from COVID-19 to donate blood plasma

  https://www.washingtonpost.com/health/2020/07/30/trump-urges-people-who-have-recovered-covid-19-donate-plasma/

  https://www.c-span.org/video/?474383-1/president-trump-roundtable-discussion-donating-plasma

July 29, 2020

- UPMC studying whether convalescent plasma help coronavirus patients with mild symptoms

  https://pittsburgh.cbslocal.com/2020/07/29/coronavirus-study-convalescent-plasma/

- COVID-19 trial to study convalescent plasma in outpatient setting

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https://web.musc.edu/about/news-center/2020/07/29/covid19-trial-to-study-convalescent-plasma-in-outpatient-setting

March 10, 2021

- Convalescent Plasma Strikes Out As COVID-19 Treatment
  https://www.npr.org/975365309

2021-03-10 Harris R: Convalescent plasma strikes out as COVID-19 Treatment. NPR, March 10, 2021, 5:01 AM ET

More than half a million Americans have received an experimental treatment for COVID-19 called convalescent plasma. But a year into the pandemic, it's not clear who, if anyone, benefits from it.

That uncertainty highlights the challenges scientists have faced in their attempts to evaluate COVID-19 drugs.

On paper, treatment with convalescent plasma makes good sense. The idea is to take blood plasma from people who have recovered from COVID-19 and infuse it into patients with active infections. The antibodies in the donated plasma, in theory, would help fight the virus.

Based on that idea, last March Dr. Nicole Bouvier at the Icahn School of Medicine at Mount Sinai Hospital in New York decided to give it a try.

She recalls thinking, "we have this new disease that didn't have any known therapies, and convalescent plasma has been used in new epidemic and pandemic diseases," as recently as in an Ebola outbreak in West Africa a few years ago.

She says she was the first doctor to get special permission from the Food and Drug Administration to use it as an experimental treatment.

It was a huge commitment to line up people willing to donate plasma as well as to treat patients themselves, "so it was a big production," she says. "We ultimately screened over 70,000 people" and identified around 20,000 who had high antibody levels in their blood plasma.

Mount Sinai treated more than 1,400 patients, including throughout the height of New York City's nightmarish COVID-19 outbreak last spring. But all the while Bouvier had no idea whether the plasma really worked.

Finally, a couple of weeks ago, she had seen enough data from carefully controlled studies — and decided to stop offering the treatment.

"The straw that broke the camel's back was two very large cohort trials," she says.

The RECOVERY Trial in the United Kingdom had studied more than 10,000 volunteers and found no benefit. Another one called CONCOR-1, run by Canadians, had studied nearly 1,000 patients. It, too, stopped recruiting new patients because doing so would have been futile.

But those studies focused on people sick enough to be in the hospital. Dr. Arturo Casadevall at the Johns Hopkins Bloomberg School of Public Health is one of the prime advocates for convalescent plasma. He says he thinks the treatment needs to be done sooner, in the outpatient setting.

"From the very beginning here at Hopkins we set out to do outpatient trials," he says. "The trials were set up in March [of 2020], however it took many months to get the money to do it." With taxpayer money nowhere to be found, the study ultimately went forward with funding from the billionaire Michael Bloomberg, Casadevall says.

A year later, the study at Hopkins still doesn't have results. And it's not just a question of funding. The entire U.S. medical research system isn't set up to do what's needed to identify new treatments during a pandemic.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

Dr. Derek Angus, chair of critical care medicine at the University of Pittsburgh, says that in a public health emergency scientists should be able to evaluate new treatments at hundreds of hospitals, in a matter of months.

"People might roll their eyes and say that's impossible, but that's largely what the United Kingdom has done," Angus says. "For all our capacity in the United States, it's depressing that we can't do a U.S. version."

The U.K. was able to launch its vast study quickly because Britain has a national health system that not only provides treatment but can conduct research. Research in the U.S. is balkanized among universities, drug companies and funders.

"We pride ourselves on having a very federated, independent system," Angus says. "But, gosh, that is very hard to turn on a dime to solve national problems."

To give just one example, a national network of emergency room physicians got federal funding to treat people with convalescent plasma, in a study named C3PO. Their patients were sick enough to show up in the emergency room, but well enough to go home afterward.

"We should have been able to get this done as quickly as they did in the U.K.," says Dr. Kevin Schulman at Stanford University. "It was just a much slower process to set up."

Schulman at Stanford was responsible for some of the logistics. And they were a nightmare, he says.

"I said tongue in cheek at some point when we had five patients in our study that we had at least 500 people touch a paper for the five patients we had recruited. And that's the opposite in the UK."

"Some of the contracts for the trial we are still negotiating even today," he adds. "You know, the U.K. didn't have any of that."

The C3PO study recently stopped recruiting patients. It had enrolled about 500 out of a planned 900, but an independent monitoring board concluded that continuing would have been futile.

This further casts doubt on the value of convalescent plasma.

"I don't see any point in offering plasma outside a clinical trial," says Angus from Pitt.

Several trials are ongoing. And there's still a chance that some of them could identify a group of patients, treated at a particular time with a particular concentration of plasma, who would benefit. So Bouvier at Mount Sinai hasn't given up on it completely.

In retrospect, it's understandable why convalescent plasma doesn't help people hospitalized with significant illness, she says. Serious illness is caused primarily by the body's reaction. Respiratory viruses like these don't persist for long. "They're sort of like, 'wham, bam, thank you, ma'am.' And then they're gone," Bouvier says.

"If a study comes along that identifies a population in whom convalescent plasma is useful, we will use it in that population" she says.

And if it does appear to be helpful for people who are early in the course of disease, that raises another question: Would plasma be better than the monoclonal antibody drugs already authorized by the Food and Drug Administration for that purpose and easier to use?

Casadevall at Hopkins argues that plasma might be better, especially if new virus variants can evade the antibody drugs. Antibodies in the plasma of people who have recovered have apparently been successful in controlling whatever virus they encountered, so the treatment actually evolves along with the pandemic.

But to figure out whether convalescent plasma is better than monoclonal antibodies could require another large, time-consuming study in a research system not set up to be nimble.

You can contact NPR Science correspondent Richard Harris at rharris@npr.org.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

786) 2021-03-04 United States Government / Mayo Clinic: Historical EAP program participation. [EAP=Expanded Access Program = Compassionate Use Program]. March 4, 2021. https://www.uscovidplasma.org/

787) 2021-03-05 Woodward A, DeAngelis A: A future COVID-19 vaccine could be squirted up the nose. The nasal spray could stop transmission, especially in kids. https://www.businessinsider.com/intranasal-covid-19-vaccine-spray-could-stem-spread-2021-3

788) 2021-03-06-10 Levin J: Remdesivir versus standard of care for severe COVID-19. Conference on Retroviruses and Opportunistic Infections, Boston, MA, March 6-10, 2021. https://natap.org/2021/CROI/croi_197.htm

789) 2021-03-6-10 Dougan M, Nirula A, Gottlieb RL, Azizad M, Mocherla B, Chen P, Huhn G, Adams AC, Schade AE, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM, for BLAZE-1 Investigators: Bamlanivimab+Eteseviman for treatment of COVID-19 in high-risk ambulatory patients. Conference on Retroviruses and Opportunistic Infections, Boston, MA, March 6-10, 2021. https://natap.org/2021/CROI/croi_71.htm

BLAZE-1 Phase 3: Summary

Phase 3 confirms and replicates Phase 2 findings, with 70% reduction in risk of hospitalization ($p=0.0004$), decreased viral load ($p<0.001$), and improved sustained symptom resolution ($p=0.007$)

Outcomes consistent with EUA for bamlanivimab alone (71% reduction in risk of hospitalization)

No death due to any cause (Placebo: 10 vs. bamlanivimab + etesevimab together: 0)

Clinically meaningful results reflect the potential of bamlanivimab and etesevimab together in offering strong protection to the most vulnerable patients

Results support the potential for neutralizing monoclonal antibody therapy to reduce mortality, burden on the health care system, and duration of symptomatic disease in infected high-risk individuals

790) 2021-03-06 through 10 Mascolini M: Convalescent plasma has no effect on survival or disease course with severe COVID-19. Conference on Retroviruses and Opportunistic Infections, Boston, MA, March 6-10, 2021. https://natap.org/2021/CROI/croi_70.htm

Convalescent plasma from people with COVID-19 did not prolong survival, improve disease course, or affect virologic or immunologic markers of people receiving the plasma during severe disease [1]. Results of this 87-person open-label randomized trial in the Netherlands suggested to the researchers that this therapy "should be studied as early as possible in the disease course or at least preceding the start of an autologous humoral response."

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

791) 2021-03-06 through 10: (Reported by Jules Levin), Olender S, Walunas TL. Martinez E, Boffito M, Perez KK, Castagna A, Wang S, Goyal P, Ripamonti D, Bernardino JI, Haubrich RH, Chokkalingam AP, Wu G, Diaz-Cuervo H, Brainard D: Remdesivir versus standard of care for severe COVID-19. Conference on retroviruses and opportunistic infections. https://www.natap.org/2021/CROI/croi_197.htm

Background: Remdesivir (RDV), a direct-acting nucleotide pro-drug inhibitor of viral RNA-dependent RNA polymerases, was approved by the FDA for the treatment of hospitalized patients (pts) with COVID-19 infection and has been shown to shorten time to recovery and improve clinical outcomes in randomized clinical trials. We present the final Day 28 (D28) analysis of RDV vs standard of care (SOC) (interim Day 14 [D14] analysis published [Olender et al. Clin Infect Dis 2020]).

Methods: Final comparative analysis from two studies: a prospective phase 3, randomized study of RDV (RDV cohort) and a real-world retrospective cohort study of SOC (non-RDV cohort). Both studies enrolled pts with SARS-CoV-2 infection confirmed by polymerase chain reaction, who had oxygen saturation â‰¤94% on room air or required supplemental oxygen and had pulmonary infiltrates. Pts in the RDV cohort were randomized 1:1 to receive IV RDV for 5 or 10 days (200 mg on Day 1 followed by 100 mg/day on Days 2â€“5 or 2â€“10), plus SOC; the two randomized dose-groups were combined for analysis. Pts in the non-RDV cohort received SOC as determined by local treatment practices (excluding RDV). Analysis populations were balanced using propensity score (PS) matching. The coprimary endpoints were D14 clinical recovery (determined using a 7-point ordinal scale) and D28 all-cause mortality. Factors associated with D28 mortality were assessed using a multivariable logistic regression model.

Results: After PS matching, baseline characteristics were generally similar in the RDV and non-RDV cohorts; median age 61 years, 63% male, 42% obese, 12% Black, 71% no/low-flow oxygen use, 25% high-flow oxygen, 3% ventilated. Pts in the RDV cohort had significantly higher D14 clinical recovery rates (65% vs 57%) and significantly lower D28 mortality rates (12% vs 16%) compared with the non-RDV cohort (Table). In the multivariable analysis, in addition to RDV use, a lower risk of death at D28 was associated with: younger age; being female; being White (versus being Black/African American); receiving an HIV protease inhibitor prior to baseline; not having cardiovascular disease or COPD; more days of symptoms prior to baseline; and being on room air or low-flow oxygen at baseline (versus being on invasive mechanical ventilation).

Conclusion: RDV was associated with significantly higher rates of clinical recovery at Day 14 and lower Day 28 mortality compared with SOC in hospitalized pts with severe SARS-CoV-2 infection.

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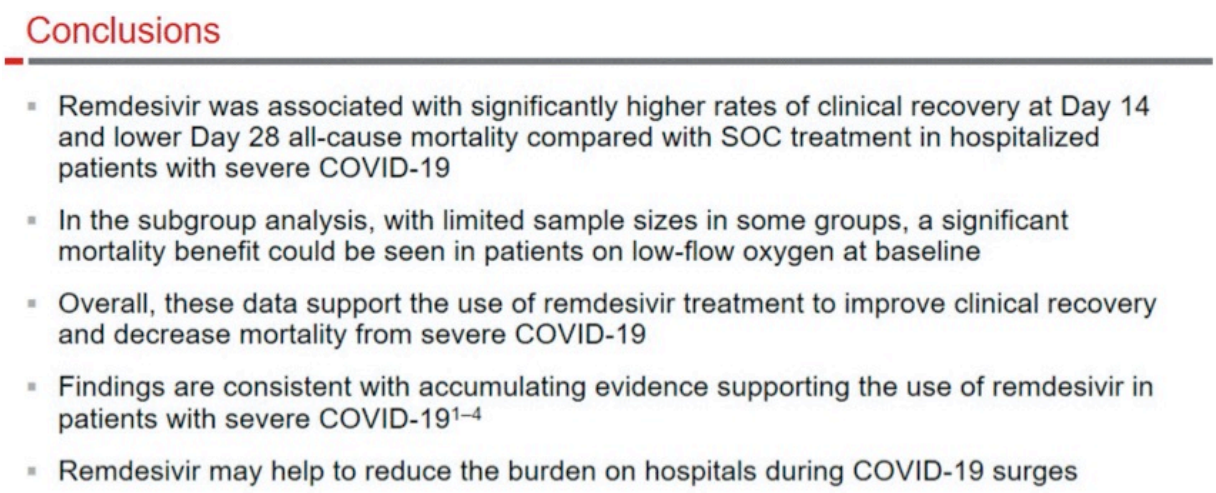
Conclusions
Remdesivir was associated with significantly higher rates of clinical recovery at Day 14 and lower Day 28 all-cause mortality compared with SOC treatment in hospitalized patients with severe COVID-19
In the subgroup analysis, with limited sample sizes in some groups, a significant mortality benefit could be seen in patients on low-flow oxygen at baseline
Overall, these data support the use of remdesivir treatment to improve clinical recovery and decrease mortality from severe COVID-19
Findings are consistent with accumulating evidence supporting the use of remdesivir in patients with severe COVID-19[1–4]
Remdesivir may help to reduce the burden on hospitals during COVID-19 surges

792) 2021-03-08 Winn K: Blood center to phase out CCP donations—Due to strong inventory, decline in COVID-19 hospitalization rate, Blood Center will phase out COVID-19 Convalescent Plasma donations March 26, 2021. https://www.bloodcenter.org/about/news/news-releases/blood-center-to-phase-out-ccp-donations/ ; https://www.bloodcenter.org/webres/File/News%20Releases/CCP%20phase%20out%20March%202021/COVID19%20CCP%20phaseout_CICBC.pdf ; and https://www.bloodcenter.org/hospitals/patient-services/convalescent-plasma/

793) 2021-03-09 Hinton DM: U.S. Food & Drug Administration Emergency Utilization Authorization (EUA) regarding COVID-19 Convalescent Plasma. https://www.fda.gov/media/141477/download

> Following the August 23, 2020, authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 use. Based on assessment of these data, **potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease**.[6] *Transfusion of COVID-19 convalescent plasma in hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit*. These considerations may be different in patients with suppressed or deficient humoral immunity.
>
> **[6]Based on what is known about the typical course of the illness and kinetics of the humoral immune response in COVID-19, for most hospitalized patients, early in the course of disease likely represents prior to respiratory failure requiring intubation and mechanical ventilation. The therapeutic window may be longer when CCP is administered to patients with clinical or laboratory evidence of impaired humoral immunity.**

794) 2021-03-09 Karamyan VT: Review: Between two storms, vasoactive peptides or bradykinin underlie severity of COVID-19? Physiol Rep 2021 Mar 9; 9(5): e14796. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7941673/pdf/PHY2-9-e14796.pdf

Abstract

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a world-wide pandemic with overwhelming socioeconomic impact. Since inflammation is one of the major causes of COVID-19 complications, the associated molecular mechanisms have been the focus of many studies to better understand this disease and develop improved treatments for patients contracting SARS-CoV-2. Among these, strong emphasis has been placed on pro-inflammatory cytokines, associating severity of COVID-19 with so-called "cytokine storm." More recently, peptide bradykinin, its dysregulated signaling or "bradykinin storm," has emerged as a primary mechanism to explain COVID-19-related complications. Unfortunately, this important development may not fully capture the main molecular players that underlie the disease severity. To this end, in this focused review, several lines of evidence are provided to suggest that in addition to bradykinin, two closely related vasoactive peptides, substance P and neurotensin, are also likely to drive microvascular permeability and inflammation, and be responsible for development of COVID-19 pathology. Furthermore, based on published experimental observations, it is postulated that in addition to ACE and neprilysin, peptidase neurolysin (Nln) is also likely to contribute to accumulation of bradykinin, substance P and neurotensin, and progression of the disease. **In conclusion, it is proposed that "vasoactive peptide storm" may underlie severity of COVID-19 and that simultaneous inhibition of all three peptidergic systems could be therapeutically more advantageous rather than modulation of any single mechanism alone.**

795) 2021-03-10 Association of American Blood Banks (AABB): Regulatory update: FDA Revises CCP EUA, Adds Abbott test. https://www.aabb.org/news-resources/news/article/2021/03/10/regulatory-update-fda-revises-ccp-eua-adds-roche-test

796) 2021-03-18 Juneja K, Humeniuk R, Porter D, Cao H, Feng J: Reply to Yan and Muler, "Remdesivir for COVID-19: Why not dose higher?" Antimicrobial Agents and Chemotherapy, 2021 April; 65(4): e1-e3. https://aac.asm.org/content/aac/65/4/e00085-21.full.pdf

797) 2021-03-18 Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiffins CC, Bruno KA, Klompas AM, Lesseer ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL: Wright RS, Casadevall A: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021 Mar 18; 384 (11): https://www.nejm.org/doi/full/10.1056/nejmoa2031893 and https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031893?articleTools=true

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

M.J. Joyner, R.E. Carter, J.W. Senefeld, S.A. Klassen, J.R. Mills, P.W. Johnson, E.S. Theel, C.C. Wiggins, K.A. Bruno, A.M. Klompas, E.R. Lesser, K.L. Kunze, M.A. Sexton, J.C. Diaz Soto, S.E. Baker, J.R.A. Shepherd, N. van Helmond, N.C. Verdun, P. Marks, C.M. van Buskirk, J.L. Winters, J.R. Stubbs, R.F. Rea, D.O. Hodge, V. Herasevich, E.R. Whelan, A.J. Clayburn, K.F. Larson, J.G. Ripoll, K.J. Andersen, M.R. Buras, M.N.P. Vogt, J.J. Dennis, R.J. Regimbal, P.R. Bauer, J.E. Blair, N.S. Paneth, D.L. Fairweather, R.S. Wright, and A. Casadevall

ABSTRACT

BACKGROUND
Convalescent plasma has been widely used to treat coronavirus disease 2019 (Covid-19) under the presumption that such plasma contains potentially therapeutic antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can be passively transferred to the plasma recipient. Whether convalescent plasma with high antibody levels rather than low antibody levels is associated with a lower risk of death is unknown.

METHODS
In a retrospective study based on a U.S. national registry, we determined the anti–SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. The primary outcome was death within 30 days after plasma transfusion. Patients who were enrolled through July 4, 2020, and for whom data on anti–SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in the analysis.

RESULTS
Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti–SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32).

CONCLUSIONS
Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Joyner at the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at joyner.michael@mayo.edu.

Drs. Joyner, Carter, and Senefeld and Drs. Paneth, Fairweather, Wright, and Casadevall contributed equally to this article.

This article was published on January 13, 2021, at NEJM.org.

N Engl J Med 2021;384:1015-27.
DOI: 10.1056/NEJMoa2031893
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799) 2021-03-23 FDA: Expanded access. https://www.fda.gov/news-events/public-health-focus/expanded-access

800) 2021-03-26 Gupta S: Autopsy of a pandemic: 6 doctors at the center of the US Covid-19 response. CNN health. https://www.cnn.com/2021/03/26/health/covid-war-doctors-sanjay-gupta/index.html

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802) 2021-03-29 Caplan AI: Placebo Controls: Now??. Arch Immunol Ther Exp (Warsz) 2021 March 29; 69 (1): 9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8006883/pdf/5_2021_Article_612.pdf

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

803) 2021-03-29 Collinson S: America's pandemic dead deserve accountability after Birx disclosure. CNN politics. https://www.cnn.com/2021/03/29/politics/coronavirus-deborah-birx-donald-trump-joe-biden/index.html

804) 2021-03-29 Howard J: "All the doctors" working on US coronavirus response received death threats, Birx says. CNN Health. https://www.cnn.com/health/live-news/covid-pandemic-doctors-cnn-special/h_c99768531e3b8232888d7684b37b539f

805) 2021-03-30. U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210330024720/https://www.fda.gov/media/141480/download

806) 2021-03-31 Hinton DM: QuickVue At-Home OTC COVID-19 Test EUA210269 https://www.fda.gov/media/147247/download

807) 2021-04 CDC: Clinical considerations: Myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults. CDC, Vaccines & Immunizations. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html

808) 2021-04 Spellberg B, Nielsen TB, Casadevall A: Antibodies, Immunity, and COVID-19. JAMA Internal Medicine 2021 April; 181 (4): 460-462. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2773575

> In summary, a robust and well-designed seroprevalence study using residual serum samples from across the US has found that herd immunity to SARS-Cov-2 is nowhere in sight, even as the COVID-19 pandemic has raged on for a year. The good news is that the limited number of reinfections of SARSCoV-2 to date, and the experience with natural infections with other viruses, suggests that protective immunity to COVID-19 should result, a harbinger for the success of vaccines. The bad news is that, like the 1918 influenza pandemic, achieving herd immunity through natural infections will take years of painful sacrifice that are tallied in numerous deaths, severe longterm health sequelae,and widespread economic disruption and hardship. Let us hope that safe and effective vaccines help avoid the consequences of naturally developing herd immunity toCOVID-19, as they have reliably done for so many other respiratory viruses.

809) 2021-04-02 Center for Constitutional Rights: Factsheet: U.S. Sanctions on the International Criminal Court. https://ccrjustice.org/factsheet-us-sanctions-international-criminal-court

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

810) 2021-04-06 Liew OW, Ling SSM, Lilyanna S, Zhou Y, Wang lP, Chong JPC, NG YX, Lim AES, Leong ERY, Lin Q, Lim TK, Lin FQ, Ng EMW, Ng TW, Richards AM: Epitope-directed monoclonal antibody production using a mixed antigen cocktail facilitates antibody characterization and validation. *Nature* communications biology 2021; 4 (Article number 441): 1-17. https://www.nature.com/articles/s42003-021-01965-x Author correction published 04 May 2021.

811) 2021-04-08 NIH COVID-19 Treatment Guidelines. The COVID-19 Treatment Guidelines Panel's statement on the Emergency Use Authorization of Anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19. **(This is copied verbatim as it is so important)**
http://web.archive.org/web/20210417040352/https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/

> **The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19**
>
> *Last Updated: April 8, 2021*
>
> Anti-SARS-CoV-2 monoclonal antibodies that target the SARS-CoV-2 spike protein and block virus entry into cells have been evaluated for the treatment of COVID-19. To date, the Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for the following anti-SARS-CoV-2 monoclonal antibodies and combinations: bamlanivimab alone, bamlanivimab plus etesevimab, and casirivimab plus imdevimab.
>
> Data are emerging on the currently available anti-SARS-CoV-2 monoclonal antibodies, including preliminary data from a Phase 3 trial of casirivimab plus imdevimab, and on the in vitro susceptibility of SARS-CoV-2 variants to anti-SARS-CoV-2 monoclonal antibodies. After reviewing the available data, the COVID-19 Treatment Guidelines Panel (the Panel) has updated its recommendations on the use of anti-SARS-CoV-2 monoclonal antibodies in outpatients with mild to moderate COVID-19 who are at high risk of disease progression. In addition, the Panel notes that, because of an increasing number of reports of variants that are resistant to bamlanivimab alone, this product will no longer be distributed by the U.S. government.[1.]

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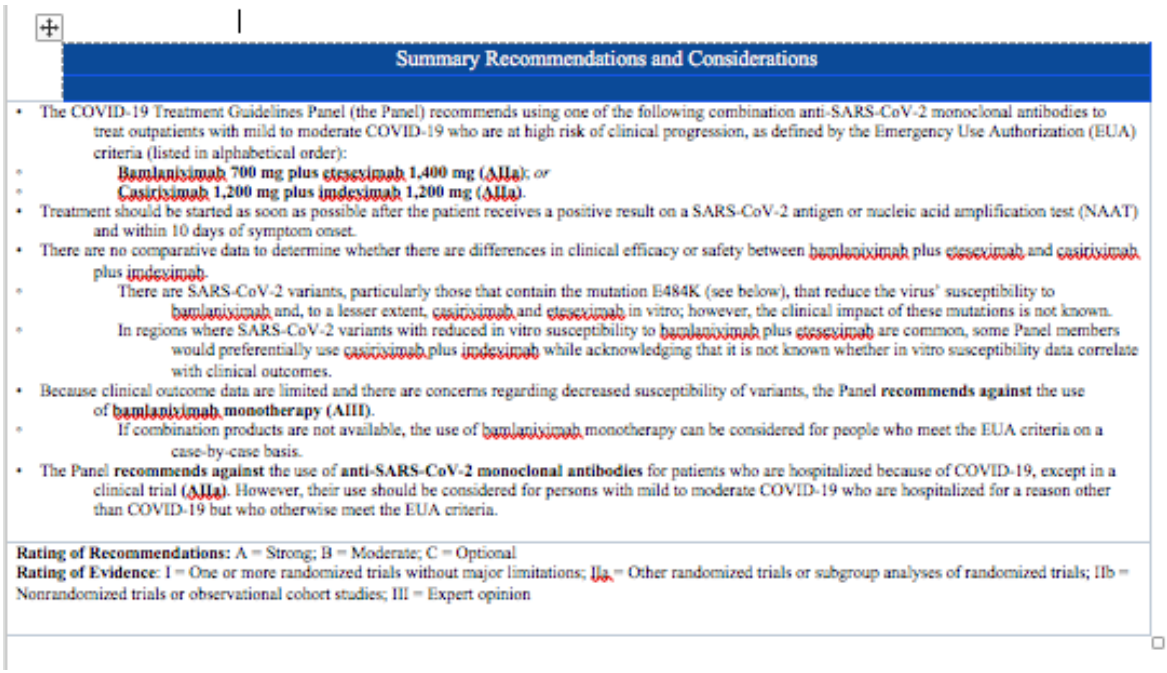

Summary Recommendations and Considerations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria (listed in alphabetical order):
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa)**; *or*
  - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa)**.
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
  - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K (see below), that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
  - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**.
  - If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial **(AIIa)**. However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

SARS-CoV-2 Variants of Concern or Interest and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab. However, the impact of these mutations on the clinical response to antibody combinations is uncertain, and the prevalence of these variants in different regions may vary.[2] Of note:

- The B.1.1.7 variant of concern, which is increasing in frequency in the United States, retains in vitro susceptibility to the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.[3-5]
- The B.1.351 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.[4,6,7] In vitro studies suggest that bamlanivimab plus etesevimab has markedly reduced activity against the B.1.351 variant.[3] In vitro studies also suggest that the K417N mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.[5]
- The P.1 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.[3,7] In vitro studies suggest that bamlanivimab plus etesevimab also has markedly reduced activity against the P.1 variant.[3,6,8] In vitro studies also suggest that the K417T mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.[5]
- The B.1.429/B.1.427 variants of concern (also called 20C/CAL.20C) that are circulating in parts of the United States, including California, Arizona, and Nevada, have the L452R mutation. This mutation is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to be a modest in vitro decrease in susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.[3]

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- The B.1.526 variant of interest is circulating in parts of the United States, such as New York. It commonly has the E484K mutation, which is associated with a marked reduction in in vitro susceptibility to bamlanivimab.3 There appears to also be reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.3 In vitro studies suggest that the E484K mutation may reduce casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.[5]
-

Ongoing population-based genomic surveillance of the types and frequencies of circulating SARS-CoV-2 variants and studies on the susceptibility of different variants to available anti-SARS-CoV-2 monoclonal antibodies will be important in defining the utility of specific monoclonal antibodies in the future.

Rationale for Recommending Bamlanivimab Plus Etesevimab
In the Phase 3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, all the participants met the criteria for being at high risk for progressing to severe COVID-19 and/or hospitalization (as defined in the EUA). A total of 1,035 participants were randomized to receive bamlanivimab 2,800 mg plus etesevimab 2,800 mg (n = 518) or placebo (n = 517).
The median participant age at baseline was 56 years; 31% of the participants were aged ≥65 years. Across the arms, 52% of the participants were women, 87% were White, 29% were Hispanic/Latinx, and 8% were Black or African American. The mean duration of symptoms at study enrollment was 4 days, and 77% of the participants had mild COVID-19.

The primary endpoint was the proportion of participants who had a COVID-19-related hospitalization (defined as ≥24 hours of acute care) or who died from any cause by Day 29. Endpoint events occurred in 11 of 518 participants (2%) in the bamlanivimab plus etesevimab arm and in 36 of 517 participants (7%) in the placebo arm. Compared to the placebo-treated participants, the participants who received bamlanivimab plus etesevimab had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause ($P < 0.001$). There were no deaths in the bamlanivimab plus etesevimab arm, and 10 deaths occurred in the placebo arm (10 of 517 participants [2%] died; $P < 0.001$).

Secondary virologic endpoints included SARS-CoV-2 levels on nasopharyngeal (NP) swab assays at different time points. Study participants who received bamlanivimab plus etesevimab had a greater and more rapid decline in virus levels than those who received placebo. The proportion of participants with persistently high viral loads (defined as a SARS-CoV-2 level >5.27 log10 copies/mL at Day 7) was 10% in the bamlanivimab plus etesevimab arm and 29% in the placebo arm ($P < 0.000001$).

Recommendations for the use of bamlanivimab plus etesevimab should be considered in the context of the following limitations:

- The doses authorized in the EUA are bamlanivimab 700 mg plus etesevimab 1,400 mg, which are different from the doses of bamlanivimab 2,800 mg plus etesevimab 2,800 mg used in the Phase 3 BLAZE-1 study. The lower dose was authorized by the FDA based on preliminary data from BLAZE-4, a double-blind, placebo-controlled, randomized Phase 2 trial.[3] The available data demonstrate that the antiviral activity of bamlanivimab 700 mg plus etesevimab 1,400 mg is similar to that of bamlanivimab 2,800 mg plus etesevimab 2,800 mg.
- The results of the Phase 3 BLAZE-1 trial have not been peer reviewed and published.
- The Panel's recommendations are based on preliminary results only, and the details on the study design, follow-up, and methods are currently limited. When peer-reviewed data for the Phase 3 BLAZE-1 trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Casirivimab Plus Imdevimab
The updated recommendation for the use of casirivimab plus imdevimab is based on Phase 3 results from the R10933-10987-COV-2067 study (the information from this study is currently available only in a press

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release, and there is currently no peer-reviewed preprint or publication).[9,10] This trial compared 1,355 participants who received casirivimab 1,200 mg plus imdevimab 1,200 mg to 1,341 participants who received placebo.

The modified full analysis set (mFAS) included participants who had a positive SARS-CoV-2 polymerase chain reaction result from an NP swab at randomization and one or more risk factors for severe COVID-19. In the mFAS cohort:

- The median participant age at baseline was 50 years. Across the arms, 35% of the participants were Hispanic/Latinx and 5% were Black or African American. The median duration of symptoms prior to enrollment was 3 days.
- COVID-19-related hospitalizations or death from any cause were reported in 18 of 1,355 participants (1.3%) in the casirivimab plus imdevimab arm and 62 of 1,341 participants (4.6%) in the placebo arm ($P < 0.0001$). This represents a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death in the casirivimab plus imdevimab treatment participants.
-

In the full analysis set, there was 1 death out of 1,849 participants in the casirivimab plus imdevimab arm and 5 deaths out of 1,843 participants in the placebo arm.

Recommendations for casirivimab plus imdevimab should be considered in the context of the following limitations:

- The results of this clinical trial have not been peer reviewed and published.
- The Panel's recommendation is based on preliminary results only, and the details on the study design, follow-up, and methods are limited. When peer-reviewed data for this trial become publicly available, the Panel will review the results and update the recommendations if necessary.
-

Rationale for Recommending Against the Use of Bamlanivimab Monotherapy

As noted above, several circulating SARS-CoV-2 variants have mutations that are associated with reduced in vitro susceptibility to certain anti-SARS-CoV-2 monoclonal antibodies that are available through EUAs. In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab alone and possibly lower sensitivity to etesevimab and casirivimab. Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon. Because this field is moving quickly, and real-time testing for variants and mutations is not currently available, it seems prudent to use therapeutic options for which reduced susceptibility to the entire regimen is less likely. Therefore, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**. If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.

Rationale for Recommending Against the Use of Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Who Are Hospitalized for COVID-19

The FDA EUAs do not authorize the use of these antibodies in patients who are hospitalized for COVID-19, although their use could be considered for patients who are hospitalized for a non-COVID-19 indication and who meet the EUA criteria for the use of these products. See Anti-SARS-CoV-2 Monoclonal Antibodies for further discussion of the clinical trial data for hospitalized patients.

Anti-SARS-CoV-2 monoclonal antibodies may be available through expanded access programs for the treatment of immunocompromised patients who are hospitalized because of COVID-19. It is not yet known whether these antibodies provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

Vaccination

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SARS-CoV-2 vaccination should be deferred for at least 90 days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.[11]

For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.[11]

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies
The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: they allow for the use of the monoclonal antibodies for the treatment of COVID-19 in nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization.[3]

High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥65 years
- Aged ≥55 years and have:
  - Cardiovascular disease; *or*
  - Hypertension; *or*
  - Chronic obstructive pulmonary disease/other chronic respiratory disease.
- Aged 12 to 17 years and have:
  - BMI ≥85th percentile for their age and gender based on the Centers for Disease Control and Prevention growth charts; *or*
  - Sickle cell disease; *or*
  - Congenital or acquired heart disease; *or*
  - Neurodevelopmental disorders (e.g., cerebral palsy); *or*
  - A medically related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation); *or*
  - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

811) 2021-04-12 Regeneron: Phase 3 prevention trial showed 81% reduced risk of symptomatic SARS-COV-2 infections with subcutaneous administration of REGEN-COV™ (Casirivimab with imdevimab) https://investor.regeneron.com/news-releases/news-release-details/phase-3-prevention-trial-showed-81-reduced-risk-symptomatic-sars#:~:text=00%20AM%20EDT-,Phase%203%20Prevention%20Trial%20Showed%2081%25%20Reduced%20Risk%20of%20Symptomatic,COV%E2%84%A2%20(casirivimab%20with%20imdevimab)

812) 2021-04-12 Regeneron: Phase 3 Prevention Trial Showed 81% Reduced Risk of Symptomatic SARS-CoV-2 Infections with Subcutaneous Administration of REGEN-COV™ (casirivimab with imdevimab). https://investor.regeneron.com/node/25016/pdf

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PHASE 3 PREVENTION TRIAL SHOWED 81% REDUCED RISK OF SYMPTOMATIC

SARS-COV-2 INFECTIONS WITH SUBCUTANEOUS ADMINISTRATION OF REGEN-

COV™ (CASIRIVIMAB WITH IMDEVIMAB)
TARRYTOWN, N.Y., April 12, 2021 /PRNewswire/ --

REGEN-COV rapidly protected household contacts from exposure to SARS-CoV-2 at home, with 72% protection against symptomatic infections in the first week, and 93% in subsequent weeks

Among individuals who developed symptomatic infections, REGEN-COV recipients cleared the virus faster and had much shorter symptom duration

Regeneron will share data with U.S. FDA and request EUA expansion to include COVID prevention for appropriate populations, using a 1,200 mg subcutaneous dose

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive results from a Phase 3 trial (2069A) assessing the ability of REGEN-COV™ (casirivimab with imdevimab) to reduce the risk and burden of COVID-19 infection among household contacts of SARS-CoV-2 infected individuals. The trial, which was jointly run with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), met its primary and key secondary endpoints, showing that REGEN-COV 1,200 mg administered subcutaneously (SC) reduced the risk of symptomatic infections by 81% in those who were not infected when they entered the trial.

"These data suggest that REGEN-COV can complement widespread vaccination strategies, particularly for those at high risk of infection. Importantly, to date REGEN-COV has been shown *in vitro* to retain its potency against emerging COVID-19 variants of concern," said Myron Cohen, M.D., who leads the monoclonal antibody efforts for the NIH-sponsored COVID Prevention Network (CoVPN) and is Director of the Institute for Global Health & Infectious Diseases at the University of North Carolina at Chapel Hill. "Despite standard precautions to reduce transmission, nearly 10% of unvaccinated individuals living with an infected person developed symptomatic infections if they did not receive REGEN-COV. If authorized, convenient subcutaneous administration of REGEN-COV could help control outbreaks in high-risk settings where individuals have not yet been vaccinated, including individual households and group living settings."

The Phase 3, double-blind, placebo-controlled trial assessed the effect of REGEN-COV on uninfected individuals without anti-SARS-CoV-2 antibodies or any COVID-19 symptoms, who lived in the same household as an individual who tested positive for SARS-CoV-2 within the prior 4 days. The trial enrolled 1,505 people who were not infected with SARS-CoV-2 at baseline and randomized to receive either 1 dose of REGEN-COV (1,200 mg) or placebo, administered as SC injections.

"These findings are very encouraging and suggest that REGEN-COV is highly effective at preventing symptomatic COVID-19 in household contacts of SARS-CoV-2 infected individuals," said Dan H. Barouch, M.D., Ph.D., co-principal investigator of the trial and Director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center and Professor of Medicine at Harvard Medical School. "The rapid and robust protection, together with the subcutaneous route of administration, support the practical utility of these antibodies in protecting

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against COVID-19 in multiple settings, including after high-risk exposures. These antibodies may be particularly useful in individuals who are not yet vaccinated, and may also have potential in those who are immunosuppressed and may not respond well to vaccines."

On average, individuals treated with REGEN-COV who experienced a symptomatic infection resolved their symptoms in 1 week, compared to 3 weeks with placebo. Infected individuals also cleared the virus faster with REGEN-COV.

"With more than 60,000 Americans continuing to be diagnosed with COVID-19 every day, the REGEN-COV antibody cocktail may help provide immediate protection to unvaccinated people who are exposed to the virus, and we are also working to understand its potential to provide ongoing protection for immunocompromised patients who may not respond well to vaccines," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "We thank the individuals, investigators and our collaborators involved in the trial, and look forward to rapidly discussing these results with regulatory authorities."

813) 2021-04-12 Regeneron: Phase 3 Prevention Trial Showed 81% Reduced Risk of Symptomatic SARS-CoV-2 Infections with Subcutaneous Administration of REGEN-COV™ (casirivimab with imdevimab). https://investor.regeneron.com/node/25016/pdf

814) 2021-04-13 Parkins K: Regeneron's antibody cocktail helps prevent and treat COVID-19 in Phase III studies. https://www.clinicaltrialsarena.com/news/regenerons-antibody-cocktail-regen-cov-helps-prevent-and-treat-covid-19-in-phase-3-studies/

815) 2021-04-14: Dutta SS: Early monoclonal antibody therapies beneficial for COVID-19, finds study. News Medical Life Sciences. Apr 14, 2021. https://www.news-medical.net/news/20210414/Early-monoclonal-antibody-therapies-beneficial-for-COVID-19-finds-study.aspx

A team of scientists recently conducted a large-scale study at Northwell Health, New York, USA, to evaluate the efficacy of neutralizing monoclonal antibody (MAB) therapies in preventing disease progression among patients with mild to moderate coronavirus disease 2019 (COVID-19). **The findings reveal that the timing of initiating MAB therapy is a crucial factor in determining its efficacy against COVID-19.** The study is currently available on the *medRxiv** preprint server.

The medRxiv* preprint server is as follows: Jarrett M, Licht WB, Bock K, Brown Z, Hirsch JS, Coppa K, Brar R, Bello S, Nash IS: Early experience with neutralizing monoclonal antibody therapy for COVID-19.
https://www.medrxiv.org/content/10.1101/2021.04.09.21255219v1.full.pdf

816) 2021-04-14 AABB: Toolkit update 04/14/2021COFVID-19 Convalescent Plasma under emergency use authorization. https://www.aabb.org/docs/default-source/default-document-library/regulatory/toolkit-for-ccp-under-eua.pdf?sfvrsn=741be857_18

817) 2021-04-14 Kummer L: Monoclonal antibodies can cut risk of hospitalization, death by 70% in COVID-19 patients. FOX 17, West Michigan.

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https://www.fox17online.com/news/local-news/kzoo-bc/kalamazoo/monoclonal-antibodies-can-cut-risk-of-hospitalization-death-by-70-in-covid-19-patients

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819) 2021-04-16. Hinton DM: Revocation the EUA for the investigational monoclonal antibody therapy bamlanivimab, *when administered alone*… https://www.fda.gov/media/147629/download

820) 2021-04-16. FDA: FDA News release: Coronavirus (COVID-19) Update: FDA revokes Emergency Use Authorization for monoclonal antibody Bamlanivimab. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab

821) 2021-04-17 Thomas K, Weiland N: The Covid-19 Plasma boom is over. What did we learn from it? *The New York Times* https://www.nytimes.com/2021/04/17/health/covid-convalescent-plasma.html finance.yahoo.com/news/ 2020-04-21 https://finance.yahoo.com/news/covid-19-plasma-boom-over-183252295.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_sig=AQAAANsdGj4POGFCOwCCvZ4XWhRaSO6gMHERUyo72az7g290KE2n3pfeL_FY2CdR6-UUXduMuGrujDf64hDPbHQ8FRjIAjEYSxQ5OratcmUofgoxaRiPA3c2ci2KFC6b9YDVJE7BqZPF_J0ff14Ften5FlbG400-F-ASWAgroYWYEv7p

> The Trump administration, buoyed by proponents at elite medical institutions, seized on plasma as a good-news story at a time when there weren't many others. It awarded more than $800 million to entities involved in its collection and administration, and put Dr. Anthony S. Fauci's face on billboards promoting the treatment.
>
> But by the end of the year, good evidence for convalescent plasma had not materialized, prompting many prestigious medical centers to quietly abandon it. By February, with cases and hospitalizations dropping, demand dipped below what blood banks had stockpiled. In March, the New York Blood Center called Mr. Cohen to cancel his 12th appointment. It didn't need any more plasma.
>
> A year ago, when Americans were dying of Covid at an alarming rate, the federal government made a big bet on plasma. No one knew if the treatment would work, but it seemed biologically plausible and safe, and there wasn't much else to try. All told, more than 722,000 units of plasma were distributed to hospitals thanks to the federal program, which ends this month.
>
> Because the government gave plasma to so many patients outside of a controlled clinical trial, it took a long time to measure its effectiveness. Eventually, studies did emerge to suggest that under the right conditions, plasma might help. But enough evidence has now accumulated to show that the country's broad, costly plasma campaign had little effect, especially in people whose disease was advanced enough to land them in the hospital.

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> In interviews, three federal health officials — Dr. Stephen M. Hahn, the former commissioner of the Food and Drug Administration; Dr. Peter Marks, a top F.D.A. regulator; and Dr. H. Clifford Lane, a clinical director at the National Institutes of Health — acknowledged that the evidence for plasma was limited.
>
> "The data are just not that strong, and it makes it makes it hard, I think, to be enthusiastic about seeing it continue to be used," Dr. Lane said. The N.I.H. recently halted an outpatient trial of plasma because of a lack of benefit.

822) 2021-04-18 U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210418170456/https://www.fda.gov/media/141480/download

823) 2021-04-19 U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://www.fda.gov/media/141480/download

824) 2021-04-21 NIH COVID-19 Treatment Guidelines: Convalescent Plasma. Last Updated: April 21, 2021. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/convalescent-plasma/

> Recommendation
> - The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**.
>   - Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.
>
> For Hospitalized Patients With COVID-19 Who Do Not Have Impaired Immunity
> - The Panel **recommends against** the use of COVID-19 **convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**.
> - The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial **(AI)**.
>
> For Hospitalized Patients With COVID-19 Who Have Impaired Immunity
> - There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
>   - Observational data including data from case reports, case series, and a retrospective case control study suggest a benefit of COVID-19 convalescent plasma in patients with various primary and secondary humoral immunodeficiencies.[2-16]
>   - Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with COVID-19 convalescent plasma.[17-19]
>   - High-titer convalescent plasma is authorized under the EUA for the treatment of hospitalized patients with COVID-19 and impaired immunity.
>
> For Nonhospitalized Patients With COVID-19
> - There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.

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- Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.
- Results from additional adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19

825) 2021-04-22 CDC: The Tuskegee Timeline. Last reviewed April 22, 2021. https://www.cdc.gov/tuskegee/timeline.htm

826) 2021-04-23 NIH COVID-19 Treatment Guidelines (First copy that eliminated Convalescent Plasma *Last updated October 9, 2020* completely as a therapeutic option.) https://web.archive.org/web/20210424024531/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

827) 2021-04-25 Auwaerter PG: Coronavirus COVID-19 (SARS-CoV-2). Johns Hopkins ABX Guide, Johns Hopkins Medicine POC-IT Guides. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_

828) 2021-04-25 Prior R: Blood banks phase out collecting convalescent plasma, but fear a US blood shortage. 58 WDJT – Milwaukee. https://www.cbs58.com/news/blood-banks-phase-out-collecting-convalescent-plasma-but-fear-a-us-blood-shortage

829) 2021-04-27 U.S. Treasury Data Lab: How is the federal government funding relief efforts for COVID-19? https://datalab.usaspending.gov/federal-covid-funding/

830) 2021-04-30 CDC & IDSA: Monoclonal antibodies. COVID-19 Real-time Learning Network. (Last update) https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies/

831) 2021-04-30 Open Society Justice Initiative: Justice initiative settles ICC Executive Order lawsuit with the Biden Administration. https://www.justiceinitiative.org/newsroom/justice-initiative-settles-icc-executive-order-lawsuit-with-the-biden-administration Download: https://www.justiceinitiative.org/uploads/df5ad29b-deec-45c5-9bab-bb1031a60bcd/osji-v-trump-et-al-4-30-2021.pdf

832) 2021-05 FDA: Fact sheet for health care providers emergency use authorization (EUA) of Bamlanivimab and Etesevimab. https://www.fda.gov/media/145802/download#:~:text=The%20U.S.%20Food%20and%20Drug,adults%20and%20pediatric%20patients%2C%20including

833) 2021-05 Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, Grossman BJ, Henderson JP, Musser J, Salazar E, Hartman WR, Bouivier NM, Liu STH, Pirofski L, Baker SE, van Helmond N, Wright RS, Fairweather D, Bruno KA, Wang Z,

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Paneth NS, Casadevall A, Joyner M: The effect of convalescent plasma therapy on COVID-19 patient mortality: Systematic review and meta-analysis. Mayo Clin Proc, 2021 May; 96 (5): 1262-1275. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7888247/pdf/main.pdf

> … Importantly, many of the patients enrolled in the studies included in the analyses received convalescent plasma transfusions later in their disease course. In this context, before antibiotics and effective vaccinations, convalescent plasma therapy was widely understood to be most efficacious very early in the course of hospitalizations.2 , [155] As a result, our analysis may underestimate the mortality reduction achievable through early administration of high-titer convalescent plasma for COVID-19.
>
> **Conclusion**
> This real-time systematic review and meta-analysis of contemporaneous studies highlights that the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19 and suggests that **early transfusion of high-titer plasma represents the optimal use scenario to reduce the risk of mortality among patients with COVID-19**. These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent.
>
> **Acknowledgments**
> The authors express their gratitude to the convalescent plasma donors.
> Drs Klassen, Senefeld, Casadevall, and Joyner contributed equally to this article.

834) 2021-05-03 Exact Sciences Corp: High sensitivity in a noninvasive **colorectal cancer (CRC) screening option**[1]. In a prospective, head-to-head, point-in-time, 90-site, pivotal study of 10,000 patients **aged 50 to 84 years at average risk for CRC**, published in *The New England Journal of Medicine,* Cologuard demonstrated[1]*: https://www.cologuardhcp.com/about/clinical-offer

835) 2021-05-04 Reuters Fact Check: Fact Check-Red Cross is accepting plasma from people vaccinated against COVID-19. https://www.reuters.com/article/factcheck-redcross-vaccinated/fact-check-red-cross-is-accepting-plasma-from-people-vaccinated-against-covid-19-idUSL1N2MR1HU

836) 2021-05-06 Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, *et al*: The Covid-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. The Lancet, Respiratory Medicine 2021 Jun; 9(6): 622-642. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8102044/pdf/main.pdf

837) 2021-05-07 Regeneron Pharmaceuticals: Safety, Tolerability, and Efficacy of Anti-spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04426695?term=REGN-COV2&cond=Covid19&draw=2&rank=3

> Regeneron Pharmaceuticals has seven studies posted on NIH https://clinicaltrials.gov and only one listed as a phase I trial (really, this is representative of the NIH designation of Phase I/II seamless trial to *de facto* avoid PL-115-176). This is legal obfuscation and complete avoidance of the intent of PL-115-176, the Right to Try Act of 2017 (signed by President Trump in 2018), which stipulates that the only requirement that must be met so that a patient can request an

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Investigational Drug or Biologic outside of a clinical trial is that a **Phase I clinical trial be "completed."** The nominal completion date of NCT04426695 on NIH https://clinicaltrials.gov is **May 7, 2021**. Conducting "seamless" Phase 1/2 or 1/2/3 Clinical Trials or Phase 2 or Phase 3 Clinical Trials without completion of a Phase 1 Clinical Trial (safety study) are ethically wrong; a violation of the stated intent of the FDA https://www.fda.gov/media/72057/download and NIH https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html standards which are contrary to these agencies' compliance with statutory mandates of the American people; and I allege that the FDA and the NIH have condoned and facilitated disregard and have violated explicitly that which is stated in PL-155-176, The Right to Try Law – **WITH REGARDS TO ALL INVOLVED PARTIES: THIS IS WRONG!**

838) 2021-05-09 Monoclonal antibodies' cocktail drug can be game changer in Covid treatment: Experts. The Times of India, May 9, 2021 https://timesofindia.indiatimes.com/city/nagpur/monoclonal-antibodies-cocktail-drug-can-be-game-changer-in-covid-treatment-experts/articleshowprint/82487621.cms

Nagpur: Experts here are expecting the antibody cocktail drug for Covid-19 developed by pharmaceutical giants Roche and Regeneron to work effectively in home-isolated mild to moderate patients who are at high risk of developing severe illness. The therapy was granted emergency use authorization in India a couple of days ago.
Named 'REGN-COV2', the drug is a cocktail of two monoclonal antibodies, Casirivimab and Imdevimab. It is projected to reduce hospitalization by 70%. The drug was tried by former US president Trump after he developed Covid-19 last year.

The therapy is also being looked at something that would help those whose vaccine barrier the virus has breached. It is also expected to be effective on children above 12 years (having body weight more than 40 kg) during the projected third wave when the younger population is likely to be at greater risk of contracting the infection.

Reaserchers is the western world are strongly pushing for yet another combination of monoclonal antibodies, Eli Lilly's Bamlanivimab and Etesivimab, which have a strong data outcome on Covid patients. In March, it received US FDA approval as a potential therapy against variants of SARS-COV2.

A triple combination drug — repurposed Interferon Beta-1b with Lopinavir-Ritonavir and Ribavirin — is also projected to help in reducing the viral load and symptoms. The study has found a place in the 'The Lancet'.

According to senior physician Dr Rajesh Atal, Roche-Renegeron's REGN-COV2 needs to be given at 'entry level' or at an early stage to ensure the spike protein of the SARS-COV2 virus doesn't attaches itself to the cells of the host body. "The drug is to be given on priority to high risk patients like obese people, elderly with comorbidities, diabetic, those ailing having renal issues and so on," he said.

"The drug is expected to work effectively on patients with pre-exposure or early exposure to the disease," said Dr Atal and added, "If one monoclonal antibody fails to act on the mutant virus, the other is expected to shoot it down or reduce the risk."

Infection disease specialist Dr Nitin Shinde, said the cocktail therapy is a good solution for families where one or more members are already infected and others too are showing symptoms. "It's a well formulated 'rescue therapy' which must be administered during the incubation period before the virus gets the better of one," said Dr Shinde.

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He further said that it should be used prophylactically and prove good for those whose vaccine shield is breached. He hoped the cocktail drug would be effective on children above 12 years of age.

Roche Pharma India's managing director V Simpson Emmanuel has said the outpatient treatment of Covid patients with the therapy would 'complement' the vaccination drive in the country.

Well-known senior physician Dr Nikhil Balankhe said studies have shown that the cocktail drug, if introduced at an early stage, is an excellent combination drug to check severe manifestation of the disease.

Dr Satish Deopujari, a well-known paediatrician, feels the monoclonal antibodies would prove to be the game changer in treatment of Covid-9 in the coming days. "The hybrid antibody (combination of Bamlanivimab-Etesevimab and Casirivimab-Imdevimab) has 85% efficacy as compared to other anti-viral drugs in demand now," he said.

Dr Deopujari warned that with major pharmaceutical players set to import the drug, there could be similar chaos as seen in the case of Remdesivir, Tocilizumab, Itolizumab and Bevacizumab. He said the government and ICMR needs to start planning now to ensure only the needy patients gets the therapy.

"This drug will have high demand in the time to come. Blackmarketing and all kinds of malpractices can't be ruled out. The government needs to start working on a strategy immediately. What happened with Remdesivir shouldn't become the case with monoclonal antibody therapy too," he said.

He said the US is following a scoring pattern. "If you fit the criteria only then you would be given the injection. Similarly, we will have to define a high-risk group. There seems to be no planning yet on how it will be rolled out," said Dr Deopujari.

What is monoclonal antibody therapy

A mouse is given antigen injection having tumor cells

The tumor cells get mixed with the plasma cells already in the body to form hybridoma, a hybrid cell

The hybridoma has only one task, that is to produce antibodies

These antibodies produced in huge quantity are called monoclonal

This antibody immediately kills the novel coronavirus

How it became popular

Former US president Donald Trump was one of the early patients on whom this experimental therapy was used

When it must be given

Ideally, in the first three days or maximum up to first 10 days from onset of Covid symptoms

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Major it is administered during OPD treatment in early stage

No other drug has so far same efficacy, provided it is given in the first 3 or 10 days

Limitations

Recommended only for the high risk group like elderly patients and those with comorbidites
Cost could be Rs1 lakh or 2lakh per dose as doctors/govt will have to triage patients

In India, indiscriminate use can't be ruled out

Benefits

Prevents hospitalization of mild to moderate patients

Three months passive protection to patient

Could be given before travel or attending an event with big gathering

The cost may go down depending on the agreement with the company

At 85%, it has highest efficacy rate as on date and prevents mortality

839) 2021-05-10 McLean T: One year after racist statues toppled in Golden Gate Park, new sculptures could be erected. SFGATE https://www.sfgate.com/bayarea/article/art-installation-replacing-racist-statues-ggp-sf-16165841.php

840) 2021-05-12 Maruhashi T, Higashi Y: Pathophysiological association of endothelial dysfunctions with fatal outcome in COVID-19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8150852/pdf/ijms-22-05131.pdf

841) 2021-05-14 Recovery Collaborative Group: Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomized controlled, open-label, platform trial. The Lancet 2021 May 29; 397, Issue 10289: 2049-2059. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00897-7/fulltext Please Note the NIH Clinic Trial NCT04381936 (https://clinicaltrials.gov/ct2/show/NCT04381936) had as its Inclusion Criteria: (i) Hospitalised, (ii) SARS-CoV-2 infection (clinically suspected or laboratory confirmed), and iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial.

842) 2021-05-15 U.S. Department of Health and Human Services: COMBATCOVID: Monoclonal antibodies for high-risk COVID-19 positive patients. (above title of COMBATCOVID is: "An official website of the United States government") This is the most recent rendition of this DHHS website as the first "digital photograph of this URL" on the Wayback Machine of the Internet Archive is January 15, 2021. https://web.archive.org/web/20210115190614/https://combatcovid.hhs.gov/i-have-covid-19-

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now/monoclonal-antibodies-high-risk-covid-19-positive-patients Below is the initial excerpted paragraphs of that which follows on May 15, 2021. https://web.archive.org/web/20210515023010/https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients :

> If you've tested positive for COVID-19, one of the first questions you may have is, *What can I do to reduce the risk of getting sicker?* The good news is, there are treatments that may reduce that risk. Depending on your age, health history, and how long you've had symptoms of COVID-19, you may qualify for a promising form of treatment for the disease. It's called monoclonal antibody (mAb) treatment.
>
> Some early evidence suggests that mAb treatment can reduce the amount of the SARS-CoV-2 virus (the virus that causes COVID-19) in a person's system. This amount is known as viral load. Having a lower viral load means you may have milder symptoms thereby decreasing the likelihood of you being hospitalized.
>
> mAb treatment may help people who:
>
> - Have a positive COVID-19 test, and had symptoms for 10 days or less, and
> - Are at high risk of getting more serious symptoms.
>
> Visit the page "How Do I Know If I'm High Risk, and What Do I Do Next?" to learn more.
>
> This page describes what mAbs are, how they can prevent mild to moderate symptoms from getting worse, and what to expect if you get mAb treatment.

843) 2021-05-18 Executive Summary: COVID-19: Pathophysiology of acute disease. The Lancet, Respiratory Medicine. https://www.thelancet.com/series/COVID-19-pathophysiology

844) 2021-05-18 Wilt TJ, Kaka AS, MacDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults – A Living Review. Updated February 2021, Health Services Research & Development Service, U.S. Department of Veterans Affairs. https://web.archive.org/web/20210602174519/https:/www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.pdf

845) 2021-05-21 Series from the Lancet journals: COVID-19: Pathophysiology of Acute Disease. https://www.lancet.com/series/COVID-19-pathophysiology

> **Executive Summary**
>
> Acute respiratory manifestations are the most common feature of severe COVID-19, but extrapulmonary features of acute disease have also been reported. Emerging evidence indicates that COVID-19 has distinctive pathophysiological features that set the disease apart from respiratory failure of other origins.

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> In the first of a Series of four papers, Ignacio Rubio and colleagues provide a comprehensive review of the pathophysiology and phenotypes of COVID-19. The challenges and promise of therapeutically targeting the pleiotropic cytokine interleukin-6 are considered in the second and third papers in the Series. Finally, a fourth paper considers the contributions of viral infection of the alveolar compartment and immunothrombosis of the juxtaposed pulmonary vascular compartment in severe COVID-19. Important questions remain about the clinical complexities and underlying mechanisms of COVID-19. Directions for future research are proposed with the aim of gaining a fuller understanding of the pathophysiology of COVID-19 and subsequently improving management and outcomes for patients.

846) 2021-05-24 BETA DATALAB: The Federal Response to COVID-19: How is the federal government funding relief efforts for COVID-19? https://datalab.usaspending.gov/federal-covid-funding/

847) 2021-05-24 Moss C: I'm a vaccinated transplant recipient. I don't have antibodies. Now what? The New York Times, 2021 May 24. https://www.nytimes.com/2021/05/24/opinion/organ-transplant-covid-vaccine.html?referringSource=articleShare

848) 2021-05-24 UPMC: Monoclonal antibodies: A treatment option for COVID-19. https://www.upmc.com/coroavirus/monclonal-antibodies

849) 2021-05-24 U.S. Department of Justice. Office of the Solicitor General. https://www.justice.gov/osg/about-office

850) 2021-05-25 Colbert S: Interview of Francis Collins, M.D., Ph.D. The Late Show with Stephen Colbert. https://www.youtube.com/watch?app=desktop&v=mi5Uf-Cr73U

851) 2021-05-26 Hinton DM: Emergency Use Authorization 100 regarding Sotrovimab of GlaxoSmithKline LLC. U.S. Food & Drug Administration. https://web.archive.org/web/20210526213011/https://www.fda.gov/media/149532/download

852) 2021-05-26 FDA: Coronavirus (COVID-19) Update: FDA authorizes additional monoclonal antibody for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19

[This immediate series of references are extremely important and essential to rationalize the errant control over *Passive Immunization* by the FDA and the NIH before the American public over the last 16 months. While it seems the FDA is authorizing another monoclonal antibody in the <u>early</u> treatment arsenal of COVID-19 for the individual, the EUA

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Prevention: *Active Immunization*: Vaccines

authories *Sotrovimab* <u>ONLY as an *INVESTIGATIONAL BIOLOGIC*</u> which is consistent with the EUAs regarding COVID-19 Convalescent Plasma and Regeneron's and Eli Lilly's Monoclonal Antibody Cocktails prohibits the average American from obtaining it. In short, this means (unlike in Japan and India) an individual American who turns COVID-19 positive cannot *de facto* purchase any of these ***Passive Immunization agents*** within 72 hours of diagnosis as they are still ***INVESTIGATIONAL*** --not fully, officially authorized biologics by the FDA and the United States government. The FDA and the NIH continue to avoid the intent of (if not violate Federal Law) PL-115-176, the Right to Try Law of 2018.

*This is an <u>**Ethically Reprehensible methodology**</u> being practiced carte blanche by the agencies of U.S. Department of Health and Human Services of which you oversee, Mr. President: To withhold **Passive Immunization agents (COVID-19 Convalescent Plasma and Sera and Monoclonal Antibodies and Antibody Cocktails)** by rationing by federal misinformation and obfuscation is akin to the Tuskegee Syphilis Project of the mid-twentieth century.*]

> **Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy sotrovimab** for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. This includes, for example, individuals who are 65 years of age and older or individuals who have certain medical conditions.
>
> The safety and effectiveness of this investigational therapy continues to be evaluated for treatment of COVID-19. Sotrovimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. This treatment has not shown benefit in patients hospitalized due to COVID-19 and monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation.
>
> **"With the authorization of this monoclonal antibody treatment, we are providing another option to help keep high-risk patients with COVID-19 out of the hospital," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "It is**

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important to expand the arsenal of monoclonal antibody therapies that are expected to retain activity against the circulating variants of COVID-19 in the United States."

Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful antigens such as viruses. Sotrovimab is a monoclonal antibody that is specifically directed against the spike protein of SARS-CoV-2 and is designed to block the virus' attachment and entry into human cells.

853) 2021-05-26 Chen S: FDA authorizes third COVID antibody therapy treatment. AXIOS https://www.axios.com/covid-antibody-therapy-fda-authorization-8417a321-2d3e-4350-aaca-d909900a01ef.html

The U.S. Food and Drugs Administration on Wednesday authorized Vir Biotechnology and GlaxoSmithKline's monoclonal antibody drug treatment for early COVID infections, the agency said.

Why it matters: It's the third antibody treatment authorized for patients in the early stages of the disease who are at high risk of developing severe infections. The drug is "expected" to protect against variants, according to the FDA.

- The two companies in March said an interim study showed the drug was highly effective in reducing hospitalizations or death.
- **So far, the U.S. has purchased the treatment directly from manufacturers and offered it to patients through hospitals and health clinics, Wall Street Journal reports.**
- **Unlike its predecessors, Vir and Glaxo don't have a contract with the federal government, per WSJ. The companies will have to sell the drug commercially.**

What they're saying: "With the authorization of this monoclonal antibody treatment, we are providing another option to help keep high-risk patients with COVID-19 out of the hospital," Patrizia Cavazzoni, director of the FDA's Center for Drug Evaluation and Research, said in a statement.

"It is important to expand the arsenal of monoclonal antibody therapies that are expected to retain activity against the circulating variants of COVID-19 in the United States."

854) 2021-05-27 Burris S, Anderson ED, Wagenaar AC: The "Legal Epidemiology" of pandemic control. N Engl J Med 2021 May 27; 384 (21): 1973 – 1975. https://www.nejm.org/doi/pdf/10.1056/NEJMp2103380?articleTools=true

855) 2021-05-27 Takvorian SU, Guerra CE, Schpero WL: A hidden opportunity – Medicaid's role in supporting equitable access to clinical trials. N Engl J Med 2021 May 27; 384 (21): 1975 – 1978. https://www.nejm.org/doi/pdf/10.1056/NEJMp2101627?articleTools=true

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856) 2021-05-28 Cohen K: Opinion: If more children had gotten sick from covid, fewer Americans would have died. The Washington Post, May 28, 2021. https://www.washingtonpost.com/opinions/2021/05/28/what-if-covid-killed-more-children/ (Gamma Globulin was pooled donor serum).

> But one story feels very different. In late June 1953, Montgomery County undertook a mass inoculation campaign — not with the Salk vaccine, which was still two years from general use, but with gamma globulin, a substance made from blood plasma that was thought to confer some temporary protection against polio.
>
> The campaign began on a Tuesday. The front page of the Montgomery Advertiser carried a boxed announcement: "White or Black. Have You a Child 9 Years Old or Under? Turn to Page 3-B. The Map Shows You Where to Take Your Child. TODAY THRU FRIDAY. For the GG shot that will save it from Crippling Paralysis." …
>
> With almost no notice, every single child under 10 was taken to the correct place on the correct day for a treatment that, as the paper explained in a front-page Q&A, didn't always work but "may provide some protection against paralysis."
>
> Question 5: "Is GG a cure for polio?" Answer: "No." And still, 100 percent participation.
>
> So far that year, just 81 Montgomery County residents had contracted polio, and three children had died. And still, 100 percent participation.
>
> Today — with more than 575,000 Americans dead — there are vaccine resisters and anti-maskers and politicians who egg them on. That's already incredible. But if covid victims were mostly children? It would be inconceivable.

857) 2021-05-28 Reuters Fact Check: Fact Check-COVID-19 vaccines don't strip people of their antibodies; vaccinated individuals can donate blood. https://www.reuters.com/article/factcheck-vaccine-antibodies-plasma/fact-check-covid-19-vaccines-dont-strip-people-of-their-antibodies-vaccinated-individuals-can-donate-blood-idUSL2N2NF0YM

858) 2021-05-30 Can antibody cocktail used in Trump's treatment be 'game changer' in India's Covid fight? The Times of India, May 30, 2021, 1-13. https://timesofindia.indiatimes.com/india/how-low-cost-antibody-cocktail-can-be-game-changer-in-indias-covid-fight/articleshow/83089132.cms

> NEW DELHI: Last week, an 84-year-old man from Haryana was administered the "famous" anti-Covid cocktail that was also given to former US President Donald Trump.
>
> The monoclonal antibody cocktail has been touted as a "game-changer" in the fight against Covid. Studies have shown that 80% of patients who took the drug did not need hospitalisation.
>
> The most famous example was Trump himself who tested positive last year. Within, he was back at work.

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However, the cost of the drug remains expensive.

Cipla is marketing the drug in hospitals at an estimated price of Rs 59,000 *[~$800 US]* per dose. Only one dose is needed.

'A game changer'
In an interview to ANI, Dr Arvinder S Soin of the Medanta Hospital said that production of the monoclonal antibody drug at a reasonable in India could be a "game changer" for the country.

"If these (Monoclonal antibody drug) are made in large enough quantities at a reasonable price. The monoclonal antibodies could be a game changer for India and the world, and especially for high-risk elderly patients and children. There may come a time of the year when anyone testing positive can have monoclonal antibodies, and to avoid serious disease, we should adopt these early," Dr. Soin said.

He pointed out that three specific drugs (monoclonal antibodies drug) authorised by the US Food and Drug Administration (FDA) and one by India's Central Drugs Standard Control Organisation (CDSCO) can 'nip Covid infection in the bud'.

Dr. Soin said that the drug must be given soon after the patient tests positive, and most certainly in the first week of the infection.

This, can prevent severe disease and deaths.

859) 2021-06-01 Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, et al. The COVID-19 puzzle: Deciphering pathophysiology and phenotypes of a new disease entity. The Lancet, The Lancet-Respiratory Medicine SERIES, COVID-19: Pathophysiology of acute disease. June 1, 2021; 9(6), P622-642. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8102044/pdf/main.pdf

860) 2021-06-04 FDA: FDA approves drug to treat smallpox. Disease considered eradicated in 1980 but drug development for smallpox is an important component for medical countermeasure response. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-smallpox

861) 2021-06-04 Casadevall A, Dragotakes Q, Johnson PW, Senefeld JW, Klassen SA, Wright RS, Joyner MJ, Paneth N, Carter RE: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. eLife 2021; 10e69866. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205484/pdf/elife-69866.pdf

Abstract: ***(Extremely Important!)***
…Changes in the number of hospital admissions, SARS-CoV-2 variants, and age of patients could not explain these findings. The retreat from CCP might have resulted in as many as 29,000 excess deaths from mid-November 2020 to February 2021.
Conclusions: A strong inverse correlation between CCP use and mortality per admission in the USA provides population-level evidence consistent with the notion that CCP

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reduces mortality in COVID-19 and suggests that the recent decline in usage could have resulted in excess deaths.

862) 2021-06-07 Terada M, Kutsuina S, Togano T, Saito S, Kinoshita N, Shimanishi Y, Suzuki T, Miyazato Y, Inada M, Nakamoto T, *et. al.*: How we secured a COVID-19 convalescent plasma procurement scheme in Japan. Transfusion 2021 June; 61 (7): 1998-2007. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8242376/pdf/TRF-9999-0.pdf

863) 2021-06-07 U.S. Food and Drug Administration: FDA grants accelerated approval for Alzheimer's drug. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug

> Under the accelerated approval provisions, which provide patients suffering from the disease earlier access to the treatment, the FDA is requiring the company, Biogen, to conduct a new randomized, controlled clinical trial to verify the drug's clinical benefit. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.
>
> > **BUT on** 2021-06-10: Joseph A: Third member of FDA expert committee resigns over controversial Alzheimer's therapy decision. STATnews https://www.statnews.com/2021/06/10/third-member-of-fda-expert-committee-resigns-over-controversial-alzheimers-therapy-decision/

864) 2021-06-10 Callahan MV, Poznansky MC: The vaccines we have are good. But they could be so much better. The New York Times, June 10, 2021. https://www.nytimes.com/2021/06/10/opinion/covid-vaccine-strategies.html

865) 2021-06-10 California Department of PublicHealth: Monoclonal antibody treatment information for providers and facilities. https://web.archive.org/web/20210826051841/https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/Monoclonal-Antibody-Treatment-Information-for-Providers-and-Facilities.aspx

866) 2021-06-12 Mohanty KK: COVID-19 treatment: Antibody cocktail used to treat Donald Trump is helping patients in India; here's how—Monoclonal antibodies are targeted towards countering a specific antigen, which is nothing but a foreign element that the immune system recognizes to be a threat. Firstpost https://www.firstpost.com/health/covid-19-treatment-antibody-cocktail-used-to-treat-donald-trump-is-helping-patients-in-india-heres-how-9709411.html

867) 2021-06-15 Steven Colbert: The Late Show with Stephen Colbert on June 15, 2021. https://www.youtube.com/channel/UCMtFAi84ehTSYSE9XoHefig

> New York and California announced the end of virtually all pandemic restrictions after both states achieved 70% vaccination, while businesses nationwide continue to drop performative sanitation measures like excessive disinfecting of surfaces

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

868) 2021-06-16 Kupferschmidt K: Monoclonal antibodies cut risk of dying from COVID-19—but only in some patients. Science https://www.sciencemag.org/news/2021/06/monoclonal-antibodies-cut-risk-dying-covid-19-only-some-patients

Monoclonal antibodies cut risk of dying from COVID-19—but only in some patients

By **Kai Kupferschmidt**Jun. 16, 2021, 1:00 AM

***Science*'s COVID-19 reporting is supported by the Heising-Simons Foundation.**

The world's largest trial of COVID-19 therapeutics has for the first time produced convincing evidence that a therapy that directly attacks the virus can save hospitalized patients from death. A combination of antibodies called casirivimab and imdevimab, produced by Regeneron, did not lower mortality when all patients in the study were taken together, investigators of the United Kingdom's Recovery trial announced today—but it reduced deaths by one-fifth among those who did not produce antibodies themselves. A paper with the results will be made available on the medRxiv preprint server later today, the researchers say.

"Here you have really the first direct SARS-CoV-2 drug," says Eric Topol, director of the Scripps Research Translational Institute. Two drugs previously shown to reduce mortality from COVID-19 were developed for other diseases and work by dampening an overactive immune response, which is "kind of an indirect strategy," Topol says.

But Regeneron's antibodies, which attach to the receptor-binding domain of the spike protein and prevent the virus from entering cells, are expensive and not widely available, and quickly identifying patients that benefit from it may be a challenge.

Researchers have developed several monoclonal antibodies against SARS-CoV-2, with mixed results. Some, including Regeneron's, have shown some positive effects on disease progression in outpatients, but none was demonstrated to save the lives of severely ill patients in the hospital. The Recovery trial started to evaluate Regeneron's cocktail in mid-September 2020. By late May, 9785 patients had been randomly allocated to receive either the usual care in the United Kingdom or the usual care plus a one-time infusion of the two antibodies, a procedure that takes roughly 1 hour.

About one-third of the patients were seronegative when they entered the trial, meaning they did not produce antibodies themselves. That includes people with underlying health conditions that weaken their immune system, but also people who, for unclear reasons, are unable to produce antibodies early on. In this group, 30% of patients given standard care died, versus 24% of those who received the antibody cocktail. That translates to six lives saved for every 100 such patients treated with the drug.

The Regeneron cocktail received a lot of attention when former U.S. President Donald Trump received it during his bout with COVID-19 in October 2020. Although it's not clear whether Trump's immune system produced antibodies, the new results suggest the treatment may have helped save his life, Topol says: "Who knows what might have happened at his age, with his morbid obesity and all the other risk factors that he had."

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
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Although it **received an emergency use authorization** from the U.S. Food and Drug Administration in November 2020—and the **U.S. government bought 1.5 million doses**—Regeneron's therapy has not been widely used in the United States, Topol says. "This is just sitting on shelves," he says. "I think [the Recovery trial] is going to wake people up as to the benefit."

But doctors will have to determine which patients fail to produce antibodies. "I think this isn't a complicated test to run, it just needs to be done," says Martin Landray of the University of Oxford, one of Recovery's principal investigators.

A bigger challenge may be cost. "We anticipate, but we don't know this, that they may be around £1000 or £2000 per treatment," Recovery co-investigator Peter Horby said at a press conference on Tuesday. That might put the therapy and many similar ones in the pipeline out of reach for most people living in developing countries, which also have far fewer COVID-19 vaccine doses than rich countries. Access to antibody drugs in general has been particularly unequal across the globe, says Lindsay Keir, a pediatrician who co-authored **a Wellcome Trust report on global access to such treatments** released last year. "Antibodies that we have benefited from in high-income countries for 20, 30 years, still aren't available in many countries," Keir says.

The inequity is a "scandal," Horby says. "There really must be an initiative to make these drugs accessible, and that requires two things: They have to be available, which means we have to scale up manufacturing, and they have to be affordable, which means we have to reduce the prices."

869) 2021-06-16 Ellyatt H: Regeneron antibody 'cocktail' can save lives in hospitalized Covid patients, study finds. CNBC. https://www.cnbc.com/2021/06/16/regeneron-antibody-cocktail-can-save-lives-in-hospitalized-covid-patients.html

Regeneron antibody 'cocktail' can save lives in hospitalized Covid patients, study finds

PUBLISHED WED, JUN 16 20215:42 AM EDT UPDATED WED, JUN 16 20217:06 AM EDT

KEY POINTS

- Another potentially life-saving treatment for hospitalized Covid-19 patients has been discovered by researchers at the University of Oxford.
- An antibody combination made by Regeneron reduces the risk of death when given to patients with severe Covid who have not mounted a natural antibody response of their own.
- The study was part of the wider Recovery trial investigating various possible treatments for people hospitalized with coronavirus.

LONDON — Another potentially life-saving treatment for hospitalized Covid-19 patients has been discovered by researchers at the University of Oxford.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

The British study — part of the wider Recovery trial investigating various possible treatments for people hospitalized with coronavirus — found that an antibody combination made by Regeneron reduces the risk of death when given to patients with severe Covid who have not mounted a natural antibody response of their own.

The treatment uses a "cocktail" of two monoclonal antibodies (casirivimab and imdevimab, known as Regen-Cov in the U.S.) that bind specifically to two different sites on the coronavirus spike protein, neutralizing the ability of the virus to infect cells.

Previous studies in nonhospitalized Covid patients have shown that the treatment reduces viral load, shortens the time to the resolution of symptoms, and significantly reduces the risk of hospitalization or death.

But in a small trial in hospitalized patients, preliminary evidence suggested a clinical benefit for patients who had not mounted a natural antibody response of their own (that is, they were seronegative) when they entered the trial.

This latest study is the first trial large enough to determine definitively whether this treatment reduces mortality in patients hospitalized with severe Covid.

The trial, which took place between September and May, involved 9,785 patients hospitalized with Covid.

For patients who were seronegative at the start of the study, the antibody combination significantly reduced their chances of dying by one-fifth compared with those receiving usual care alone (that is, 24% of patients in the antibody combination group died versus 30% of patients in the usual care group).

Thus, for every 100 such patients treated with the antibody combination, there would be six fewer deaths.

As well as reducing the risk of death, for the seronegative patients who received the antibody combination treatment, the duration of hospital stay was four days shorter than for those receiving usual care. The chances of needing a ventilator was also lower.

The treatment had no noticeable beneficial effect on patients who were seropositive at the start of the trial.

The preliminary results from the trial, which will soon be submitted to a leading peer-reviewed medical journal, could determine how Covid patients are treated in future in hospital, one expert noted.

"It means that patients being hospitalised with Covid-19 can be divided into two groups based on whether or not they have made antibodies to the virus," Fiona Watt, executive chair of the U.K.'s Medical Research Council, said in a statement.

"If they do not have antibodies then treatment with antibody-based drugs to the spike protein can reduce their risk of death and also time spent in hospital. Patients who have made their own antibodies to the virus do not benefit from the new treatment, which is important information given the cost of drugs."

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Peter Horby, professor of emerging infectious diseases in the Nuffield Department of Medicine at the University of Oxford, and the joint chief investigator for the Recovery trial, described the results as "very exciting."

"The hope was that by giving a combination of antibodies targeting the SARS-CoV-2 virus we would be able to reduce the worst manifestations of Covid-19. There was, however, great uncertainty about the value of antiviral therapies in late-stage Covid-19 disease. It is wonderful to learn that even in advanced Covid-19 disease, targeting the virus can reduce mortality in patients who have failed to mount an antibody response of their own," he said in a statement.

The Recovery trial has already made several life-saving discoveries, one being that dexamethasone, a cheap and widely used steroid, was able to save lives among severely ill Covid patients. Last week it published the results of another trial that showed aspirin did not improve the survival rates for patients hospitalized with Covid who are at an increased risk of blood clots.

870) 2021-06-16 Olszewska-Parasiewicz J, Szarpak L, Rogula S, Gasecka A, Szymanska U, Kwiatkowsha M, Jaguszewski MJ, Sierpinski R, Zaczynski A, Wierzba W, Kosior DA: Statins in COVID-19 Therapy. Life 2021; 11, 565. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8234902/pdf/life-11-00565.pdf

871) 2021-06-20 Dickerson J: John Dickerson interviews Scott Gottlieb, M.D. on Face the Nation, June 20, 2021. https://www.cbsnews.com/news/transcript-scott-gottlieb-face-the-nation-06-20-2021/

DR. GOTTLIEB: That's right, and I think that this could be a real game changer. **This is a virus that we should be able to drug. The machinery that this virus uses to replicate are things that we've drugged before. It's not a- it's not a very wily virus. It's not a virus that should evade our drug development tools. So I think that we will have a drug that inhibits viral replication.** Pfizer, the company I'm on the board of, is working on one. Merck is working on another one in advanced development. There's a number of other companies also engaged in this pursuit. **I think we will get a drug that inhibits viral replication that could be taken on an outpatient basis and is basically like a Tamiflu for coronavirus that you could take when you first have symptoms, when you first have a diagnosis to prevent the progression to disease.**

872) 2021-06-21 Merrilles A: Washington U researchers show COVID-19 treatment often effective against virus variants, in study of rodents. The St. Louis Post-Dispatch https://www.stltoday.com/news/local/metro/washington-u-researchers-show-covid-19-treatment-often-effective-against-virus-variants-in-study-of/article_34089b54-7f2e-549a-904d-c4dacbffa031.html

i. Several monoclonal antibody treatments are currently available in the U.S. under emergency use authorization from the FDA. They are injected as early as possible during a patient's illness, and are often used for patients in more vulnerable groups, who are at higher risk of eventually having severe cases.

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873) 2021-06-21 CDC: Multisystem inflammatory syndrome in children (MIS-C) and Adults (MIS-A). https://www.cdc.gov/mis/about.html

CDC: 2021-02-24 For Parents: Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19

874) 2021-06-25 Kansteiner F, Sagonowsky E: Lilly's COVID antibody combo halted nationwide, dealing huge blow to blockbuster program. FIERCE Pharm. https://www.fiercepharma.com/pharma/lilly-s-covid-antibody-combo-halted-nationwide-dealing-huge-blow-to-blockbuster-program

875) 2021-06-28 Bhandari T: COVID-19 vaccines generates immune structures critical for lasting immunity—Vaccines likely strong, persistent immunity to COVID-19. Washington University School of Medicine. https://medicine.wustl.edu/news/covid-19-vaccine-generates-immune-structures-critical-for-lasting-immunity/

876) 2021-06-29 wcg FDANews: U.S. Suspends distribution of Eli Lilly COVID-19 Antibody Cocktail. https://www.fdanews.com/articles/203368-us-suspends-distribution-of-eli-lilly-covid-19-antibody-cocktail

877) 2021-07-01 Ashbrook M: Only 31 vaccinated Texans have died from COVID-19, DSHS data says. Over 10,000 people have died from the virus in Texas in 2021. The coronavirus vaccine became available to all adults in Texas on March 29. https://www.kvue.com/article/news/health/coronavirus/31-covid-19-deaths-in-texas-in-2021-were-of-vaccinated-individuals/269-8c6a7c82-fbde-4b2e-8f4d-694018f17276

878) 2021-07-08 NIH—COVID-19 Treatment Guidelines, Clinical Management Summary, Last Updated: July 8, 2021, pages 40-42. https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

Clinical Management Summary

Last Updated: July 8, 2021

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness. Figure 1 provides guidance for clinicians on the therapeutic management of nonhospitalized adult patients. This includes patients who do not require hospitalization or supplemental oxygen and those who have been discharged from an

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Prevention: *Active Immunization*: Vaccines

emergency department or a hospital. Figure 2 provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements.

Figure 1. Therapeutic Management of NonHospitalized Adults with COVID-19

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[a] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[d]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events **(BIII)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for further discussion. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] In laboratory studies, some SARS-CoV-2 variants of concern or interest harbor certain mutations that are associated with reduced susceptibility to certain agents. Some regimens may be preferred in certain settings based on the degree of reduced susceptibility and the prevalence of these variants in a given region. See Anti-SARS-CoV-2 Monoclonal Antibodies and the Panel's statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies for more information. Updates on the distribution of bamlanivimab plus etesevimab are available on the HHS Bamlanivimab/Etesevimab website.
[b] There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.
[c] These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.
[d] In cases where resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient and provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: ED = emergency department; EUA = Emergency Use Authorization; HHS = Department of Health and Human Services; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

COVID-19 Treatment Guidelines 41

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Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(BIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.
[b] The dose for remdesivir is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, IMV, or ECMO, remdesivir should be continued until the treatment course is completed.
[d] The dose for dexamethasone is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
[e] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.
[f] As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
[g] The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge (refer to Table 4c for dose modifications for patients with renal impairment). Baricitinib should be used in combination with steroids (with or without remdesivir). The combination of baricitinib plus tocilizumab has not been studied, and the Panel **recommends against** the use of this combination, except in a clinical trial **(AIII)**.
[h] The dose for tocilizumab is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. The combination of tocilizumab plus baricitinib has not been studied, and the use of this combination should be avoided outside of a clinical trial. See the Interleukin-6 Inhibitors section for more information.
[i] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

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> DR. FAUCI: Well, I think maybe all of the above, you know, it is almost inexplicable why people, when they see the data in front of them that they don't get vaccinated. We have a Delta variant that you mentioned, John, that is easily transmissible much more easily and readily and efficiently from person to person than the other viruses, the other variants that we've dealt with. That's the first thing. The second thing, the data that's hitting you right between the eyes is that ninety nine point five percent of all the deaths to COVID-19 are in unvaccinated people.

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> We're talking history-making, world-saving efficacy. A new Yale study estimates that, by the end of June, coronavirus vaccines had prevented approximately 279,000 deaths in the United States alone. Rochelle Walensky, director of the Centers for Disease Control and Prevention, said that in

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ABSTRACT

RESULTS

Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.

CONCLUSIONS

Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur.

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> REGEN-COV may only be used in adult and pediatric individuals (12 years of age and older weighting at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or deaths, and are:
>
> Not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications **and**
> have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease control and Prevention **or**
> who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARSp-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).
>
> …only be used in adult and pediatric individuals (12 years of age and older weighting at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or deaths, and are

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> ## Clinical Management Summary
> *Last Updated: July 8, 2021*
>
> Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

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>
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>
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> More than 93.8 percent of the U.S. is at substantial or high level of risk for community transmission of SARS-CoV-2, according to the Centers for Disease Control and Prevention (CDC). CDC defines an area to be at high risk when either the number of new cases in a county exceeds 100 per 100,000 persons, or more than 10 percent of COVID-19 tests come back positive in the past seven days. In those areas, CDC recommends wearing a mask indoors in public to maximize protection from the Delta variant and prevent spreading it to others.

919) 2021-08-20 UPMC: Monoclonal Antibodies: A treatment option for CVOID-19. Printed out 8/20/2021. https://www.upmc.com/coronavirus/monoclonal-antibodies

920) 2021-08-23 Malarkey MA, Gruber MF: Biologics License Application approval for Comirnaty, Pfizer-BioNTech COVID-19 mRNA Vaccine: BL 125742/0. https://www.fda.gov/media/151710/download

921) 2021-08-23 Hinton DM: Reissues the EUA for the Pfizer COVID-19 Vaccine to clarify the issue of the BLA 125742/0 approval. https://www.fda.gov/media/150386/download

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

> On August 23, 2021, FDA approved the biologics license application (BLA) submitted by BIONTech Manufacturing GmbH for COMIRNATY (COVID-19 Vaccine, mRNA) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.
>
> On August 23, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 12, 2021 letter of authorization in its entirety with revisions incorporated to clarify that the EUA will remain in place for the Pfizer-BioNTech COVID-19 vaccine for the previously-authorized indication and uses, and to authorize use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved BLA. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to provide update language regarding warnings and precautions related to myocarditis and pericarditis. The Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for COVID-19 Vaccine and information about the FDA-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA).
>
> Pfizer-BioNTech COVID-19 Vaccine contains a nucleoside-modified messenger RNA (modRA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 formulated in lipid particles. COMIRNATY (COVID-19 Vaccine, mRNA) is the same formulation as the Pfizer-BioNTech COVID-19 Vaccine and can be used interchangeably with the Pfizer-BioNTech COVID-19 Vaccine to provide the COVID-19 vaccination series.[8]

922) 2021-08-23 FDA: FDA approves first COVID-19 Vaccine. (Marketed as Comirnaty) https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine FDA: Comirnaty and Pfizer-BioNTech COVID-19 Vaccine https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine

> Example NBC report regarding this approval with Dr. Fauci response. https://www.nbc.com/today/video/today-in-30-august-24-dr-anthony-fauci-coronavirus-and-the-classroom/345221659

923) 2021-08-24 Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta KD, House T, Hay J, Bell JI, Newton JN, Farrar J, Crook D, Cook D, Rourke E, Studley R, Peto T, Diamond I, Walker S, the COVID-19 Infection Survey Team. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. medRxiv https://www.medrxiv.org/content/10.1101/2021.08.18.21262237v1

924) 2021-08-24 Zients J, Walensky R, Fauci A, Murthy V: Press briefing by White House COVID-19 response team and public health officials. Transcript: https://www.whitehouse.gov/briefing-room/press-briefings/2021/08/24/press-briefing-by-white-house-covid-19-response-team-and-public-health-officials-51/

> DR. FAUCI: Thank you very much, Dr. Walensky. I'd like to spend the next couple of minutes in addressing a **much-underutilized intervention for COVID-19, and that is the use of monoclonal antibodies for the TREATMENT** and **PREVENTION of SARS-CoV-2 infection and COVID-19 disease**.

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Next slide.

For those not totally familiar with this, monoclonal antibody is an antibody that's produced by a single clone of B cells or a cell line, and consists of identical antibody molecules that can actually be produced in the in-vitro situation in unlimited quantities.

Next slide.

If you look at the virion on the upper-left part of the slide and you look up the blown-up spike protein — the red molecule on the right upper panel — **when you talk about polyclonal antibodies, which result from infection or vaccination, it's a group of antibodies against every aspect of the spike protein, which is the good news. However, the concentration and the affinity of those antibodies can be markedly improved if you get a single cloned antibody — hence the word "monoclonal" — that's against the very specific part of the spike protein that can have a major effect in prevention and treatment.**

Next slide.

So, let's look at what we have. We have three anti-SARS-CoV-2 monoclonal antibody products that have currently had Emergency Use Authorization from the FDA. And the EUAs here are for adults and children 12 years of age and older who weigh at least 88 pounds.

There are three of them. There's the Lilly product — the bamlanivimab plus etesevimab. There's the Regeneron project — product, referred to as REGEN-COV. And then there's the GSK and Vir product. Each of these products targets the spike protein of SARS-CoV-2.

Next slide.

So, you can do an indication for these antibodies that are twofold. The first is to treat infection with SARS-CoV-2.

Next slide.

And in this regard, clinical trials have demonstrated that early treatment with anti-SARS-CoV-2 monoclonal antibodies can reduce the risk of COVID-19 hospitalization or death by 70 to 85 percent.

It is important to emphasize that this must be done early in infection and not wait, of course, until a person is sick enough to be hospitalized. That's when you get the best effect.

And again, being an underutilized intervention, we want people out there, including physicians, as well as potential patients, to realize the advantage of this very effective way of treating early infection.

Next slide.

Now, if you look at the people who should benefit from this, this is a list from the FDA and the NIH treatment guidelines about all of the people who may have significant benefit from this type of therapy if given early in their infection.

I'm not going to go through each and every one of them, but as you can see, there are a number of

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conditions on this slide that could benefit from the monoclonal antibody treatment after infection.

Next slide.

But there's also the benefit of prevention using monoclonal antibodies.

Next slide.

And we know now that the FDA, just a couple of weeks ago, authorized the Regeneron monoclonal antibody for post-exposure prophylaxis, namely for the prevention of COVID-19 after someone has been exposed to a documented case of SARS-CoV-2.

And even now — and I won't show the data because of lack of time — there are now studies in pre-exposure prophylaxis, as well as other studies in treatment.

So, I'll have on the last slide — next slide — the treatment guidelines panel. We can give you all the information, and it's accessible on the website shown here. And for physicians, patients, and others who want to know how you can get monoclonal antibodies administered, this is the call center and this is the online way to approach it.

So, bottom line is: This is a very effective intervention for COVID-19. It is underutilized, and we recommend strongly that we utilize this to its fullest.

YouTube (Fauci slide show: 10:22 – 15:27 minutes in presentation)
https://www.youtube.com/watch?v=AZNP05w2cxU

925) 2021-08-25 NIH/NLM: MedlinePlus—Trusted Health Information for You. Gene Therapy and Other Advances. Chapter 6: What are mRNA vaccines and how do they work? https://web.archive.org/web/20210825084027mp_/https://medlineplus.gov/download/genetics/understanding/therapy.pdf

926) 2021-08-26. Salter J: New Missouri sites announced for monoclonal antibody infusion treatments. https://www.ksdk.com/article/news/health/coronavirus/new-missouri-sites-monoclonal-antibody-infusion-treatments/63-2905c735-0e9e-41f0-99df-75ed44cd063e

927) 2021-08-26 Senator Ron Johnson: Letter to FDA Acting Commission Janet Woodcock, M.D. U.S. Senate. https://www.hsgac.senate.gov/imo/media/doc/2016-09-19%20RHJ%20to%20FDA%20Califf%20declined%20invite.pdf

In the letter that reissued the EUA for the Pfizer-BioNTech COVID-19 vaccine, the FDA stated that Comirnaty and the Pfizer-BioNTech COVID-19 vaccines are "legally distinct with certain differences that do not impact safety or effectiveness."[4] That statement, together with the fact that the FDA issued two distinct letters – one extending the EUA for the vaccine used in the U.S. and the other granting the FDA approval of the Comirnaty vaccine used in Europe and other countries – has caused a great deal of confusion.

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928) 2021-08-27 Hinton DM: ID NOW COVID-19 EUA200074 for Abbott Diagnostics qualitative detection of nucleic acid of SARS-CoV-2 virus. https://www.fda.gov/media/136522/download

929) 2021-08-27 Centers for Medicare & Medicaid Services (CMS.gov): Monoclonal antibody COVID-19 infusion. https://www.cms.gov/medicare/covid-19/monoclonal-antibody-covid-19-infusion

930) 2021-08-27 CDC, COVID-19: CDC recommends use of Johnson & Johnson's Janssen COVID-19 vaccine resume. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html

931) 2021-08-30 KMOV.COM Staff: Monoclonal antibody treatment center coming to St. Louis City. https://www.kmov.com/news/monoclonal-antibody-treatment-center-coming-to-st-louis-city/article_e1f92a34-090b-11ec-aba6-db344cba84e7.html

932) 2021-08-30 Hick JL, Hanfling D, Wynia MK, Toner E: Crisis standards of care and COVID-19: What did we learn? How do we ensure equity? What should we do? Nam.edu/Perspectives. https://nam.edu/crisis-standards-of-care-and-covid-19-what-did-we-learn-how-do-we-ensure-equity-what-should-we-do/

933) 2021-08-30 Wilt TJ, Kaka AS, MacDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults – A Living Review. U.S. Department of Veterans Affairs, Veterans Health Administration, Health Services Research & Development Service (HSR&D), Evidence Synthesis Program. https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.pdf Unable to be accessed on 1/23/2022. **But** with the Wayback Machine, one can access a 35 page document of May 18, 2021 and a 33 page document of February 17, 2021 published by VHA Health Services Research & Development Service (HSR&D). Wilt TJ, Kaka AS, McDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults – A living Review, Updated May 2021. VHA Health Services Research & Development Service (HSR&D). https://web.archive.org/web/20210602174519/https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.pdf

WHAT'S NEW

Updated May 18, 2021

Search current as of May 10, 2021

Next update expected August 31, 2021 This update revises findings from our second update of February 2021 and includes a literature search through May 10, 2021. One new small, single-center, high risk of bias RCT compared a 5-day course of remdesivir to standard of care (SC) in adults hospitalized with severe COVID-19. In per-protocol analysis, remdesivir as compared to SC did not reduce mortality, need for invasive mechanical ventilation, or frequency of adverse events. Results align with previous conclusions that remdesivir probably results in little to no difference in mortality or subsequent need for ventilation. Given the study's high risk of bias, we did not include it in aggregate certainty of evidence. ratings. Our

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original conclusions regarding certainty and strength of evidence on effectiveness of remdesivir for adults with COVID-19 remain unchanged.

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WHAT DID WE KNOW? Our prior VA-ESP report of 5 randomized trials (RCTs) concluded that in hospitalized adults with COVID-19, remdesivir probably results in little to no reduction in mortality, a moderate increase in percent recovered, and a moderate reduction in serious adverse events.1 Effects on mortality may vary by initial respiratory support but not by other patient or disease factors. Effect on hospital length of stay or percent hospitalized is mixed (3 RCTs), in part due to continued hospitalization while administering remdesivir. For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide benefits over, and fewer harms than, a 10-day course. Trials excluded pregnant women or those with severe hepatic or renal dysfunction. On October 22, 2020 the FDA approved remdesivir for patients over age 12 and weighing more than 40kg hospitalized with COVID-19.2 The FDA has noted side effects of remdesivir.3 Remdesivir is the only drug so far to receive federal approval for COVID-19. WHAT IS NEW? Updated: 05/18/2021 Search current as of 5/10/2021 This update adds 1 RCT (high risk of bias), giving a total of 6 included RCTs,4-9 and revises findings from our second update of February 2021.1 The new RCT was a small single-center study from India that compared a 5-day course of remdesivir to standard of care (SC) in adults hospitalized with severe COVID-19.9 In per-protocol analysis, remdesivir as compared to SC did not reduce mortality, need for invasive mechanical ventilation, or frequency of adverse events. Results align with previous conclusions that remdesivir probably results in little to no difference in mortality or subsequent need for ventilation. Given the study's high risk of bias, we did not include it in aggregate certainty of evidence. Summary of conclusions and updated findings are detailed in Table 1. WHAT DO WE CONCLUDE? The results of this new study did not change our prior conclusion that overall, a 10-day remdesivir course probably results in little to no reduction in mortality (4 RCTs). Remdesivir may result in a small reduction in proportion on mechanical ventilation (3 RCTs) but probably results in little to no difference in new need for ventilation versus SC (1 RCT). Remdesivir probably results in a moderate increase in percent recovered, a moderate decrease in serious adverse events, and may result in a large reduction in time to recovery. Effect on hospital length of stay or percent remaining hospitalized is mixed. Effects on mortality may vary by initial respiratory support but not by other patient or disease factors including symptom or COVID-19: Remdesivir for Adults (updated May 2021) Evidence Synthesis Program 2 hospitalization duration, age, sex, race/ethnicity, smoking status, comorbidities, geographic location, or corticosteroid use. Remdesivir may increase mortality in those already on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Recovery effects may not vary by age, sex, symptom duration, or disease severity. Remdesivir probably reduces serious adverse effects that include measures of COVID-19 disease progression. Compared with 10 days, a 5-day remdesivir course may reduce mortality and need for mechanical ventilation, may increase recovery and/or clinical improvement by small to moderate amounts, and may reduce serious adverse events among patients not requiring mechanical ventilation at baseline. Drug costs would be lower. Pregnant women, children under age 12, and individuals with severe renal and hepatic dysfunction have been excluded from studies. Caution and monitoring are indicated if remdesivir is used in these individuals. The FDA notes that remdesivir side effects include elevated liver enzymes and allergic reactions (which may include changes in blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling (eg, lips, around eyes, under the skin), rash, nausea, sweating, or shivering)

WHAT'S NEW

Updated February 17, 2021

Search current as of February 8, 2021

Next update expected April 2021 This update revises findings from our first update of November 2020 and includes a literature search through February 8, 2021. No new trials were identified. However, the largest RCT on remdesivir – Solidarity – is newly available as a peer-reviewed publication (previously available as

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

a non-peer review preprint). Our updated findings include new analyses and data on recovery/improvement, need for ventilation, hospital length of stay, and percentage of patients hospitalized between days 7- 14. We also provide new mortality analyses by subgroups.
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WHAT DID WE KNOW? Our prior VA-ESP report of 5 randomized trials (RCTs) concluded that in hospitalized adults with COVID-19, remdesivir probably results in little to no reduction in mortality, a moderate increase in percent recovered, and a moderate reduction in serious adverse events. Effect on hospital length of stay or percent hospitalized is mixed (3 RCTs) in part due to continued hospitalization while administering remdesivir.[1] For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide similar benefits to, and fewer harms than, a 10-day course. Trials excluded pregnant women or those with severe hepatic or renal dysfunction. On October 22, 2020 the FDA approved remdesivir for patients over age 12 and weighing more than 40kg hospitalized with COVID-19.[2] Remdesivir is the only drug so far to receive federal approval for COVID-19. WHAT IS NEW? Updated: 02/17/2021 Search current as of 2/8/2021 This update revises findings from our first update of November 2020 and also includes a literature search through February 8, 2021.[3] This update includes 5 RCTs, [4-8] similar to the prior report. However, the largest RCT on remdesivir – Solidarity – is newly available as a peerreviewed publication (previously available as a non-peer review pre-print).[5] Our updated findings include new analyses and data on recovery/improvement, need for ventilation, hospital length of stay, and percentage of patients hospitalized between days 7-14. We also provide new mortality analyses by subgroups defined by baseline respiratory support requirements: no oxygen, requiring supplemental oxygen but not ventilation, and requiring ventilation. Summary of conclusions and updated findings are detailed in Table 1. WHAT DO WE CONCLUDE? Overall, a 10-day remdesivir course probably results in little to no reduction in mortality (4 RCTs). Remdesivir may result in a small reduction in proportion on mechanical ventilation (3 RCTs) but probably results in little to no difference in new need for ventilation versus standard care (1 RCT). Remdesivir probably results in a moderate increase in percent recovered, a moderate decrease in serious adverse events, and may result in a large reduction in time to recovery. Effect on hospital length of stay or percent remaining hospitalized is mixed. Effects on mortality may vary by initial respiratory support but not by other patient or disease factors including: symptom or hospitalization duration, age, sex, race/ethnicity, smoking status, comorbidities, geographic location, or corticosteroid use. Remdesivir may increase mortality in those already on invasive mechanical ventilation or extracorporeal membrane oxygenation COVID-19: Remdesivir for Adults (updated Feb 2021) Evidence Synthesis Program 2 (ECMO). Recovery effects may not vary by age, sex, symptom duration, or disease severity. Remdesivir probably reduces serious adverse effects that include measures of COVID-19 disease progression. Compared with 10 days, a 5-day remdesivir course may reduce mortality and need for mechanical ventilation, and may increase recovery and/or clinical improvement by small to moderate amounts, and may reduce serious adverse events among patients not requiring mechanical ventilation at baseline. Drug costs would be lower. Pregnant women, children under age 12, and individuals with severe renal and hepatic dysfunction have been excluded from studies. Caution and monitoring are indicated if remdesivir is used in these individuals. The FDA notes that remdesivir side effects include elevated liver enzymes and allergic reactions (which may include changes in blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling (eg, lips, around eyes, under the skin), rash, nausea, sweating, or shivering).[9]

934) 2021-08-31 Merrilees A: New COCID clinics open in St. Louis area in push to keep patients out of hospitals. https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/new-covid-clinics-open-in-st-louis-area-in-push-to-keep-patients-out-of/article_04de965d-c7e2-5bd2-9b22-aff09ae37c0b.html

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935) 2021-08-31 wcg FDANEWS: FDA Reauthorizes Eli Lilly antibodies for COVID-19, but only in certain states. https://www.fdanews.com/articles/204205-fda-reauthorizes-eli-lilly-antibodies-for-covid-19-but-only-in-certain-states

936) 2021-09-01 Palermo G: St. Louis doctor says COVID antibody treatment is not a replacement for vaccines. FOX 2 now https://fox2now.com/news/st-louis-doctor-says-covid-antibody-treatment-is-not-a-replacement-for-vaccines/

937) 2021-09-02 BJC HealthCare, Washington University Physicians: COVID-19 Adult treatment guidance. https://covid19.bjc.org/Portals/0/PDF%20Documents/Clinical%20Resources/BJC_COVID-19_Treatment_Guidance_Final_1.pdf?ver=lk2wlZrR_T62_7WN0ac57A%3D%3D

938) 2021-09-02 FDA: FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COV™ (casirivimab and imdevimab) https://www.fda.gov/media/145611/download

939) 2021-09-03 Berman R: COVID-19: Monoclonal antibody combo helps high-risk people avoid hospital. MedicalNewsToday September 3, 2021 https://www.medicalnewstoday.com/articles/covid-19-monoclonal-antibody-combo-helps-high-risk-people-avoid-hospital

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941) 2021-09-03 NIH research matters: Intranasal COVID-19 vaccine effective in animal studies. https://nihrecord.nih.gov/2021/09/03/intranasal-covid-19-vaccine-effective-animal-studies

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943) 2021-09-07 Scholl J: Crisis standards of care activated for COVID-19 in North Idaho. Here's what we know. Idaho Statesman. https://www.idahostatesman.com/news/coronavirus/article254047758.html

944) 2021-09-11 Tin A: Unvaccinated people 11 times more likely to die from COVID-19, CDC study shows. CBS News September 11, 2021. https://www.cbsnews.com/news/covid-19-vaccine-deaths-unvaccinated-cdc-study/

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946) 2021-09-09 Regeneron: Dear HCP Letter REGEN-COV (casirivimab and imdevimab) https://www.regencov.com/hcp/starting-treatment

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948) 2021-09-10 McEvoy J: Nation short on supply of key Covid treatment – Desperate states told to reduce requests. Forbes Sep 10, 2021. https://www.forbes.com/sites/jemimamcevoy/2021/09/10/nation-short-on-supply-of-key-covid-treatment-desperate-states-told-to-reduce-requests/?sh=760dfa9e6737

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950) 2021-09-13 ASPR, Assistant Secretary for Preparedness and Response: Expanding Access to COVID-19 Therapeutics HHS PREP Act Declaration: 9th Amendment. DHHS. https://www.phe.gov/Preparedness/legal/prepact/Pages/PREPact-NinethAmendment.aspx

https://www.phe.gov/Preparedness/legal/prepact/Documents/PrepAct-Declaration-Amendment-FactSheet-8sept2021.pdf

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954) 2021-09-16 Hinton DM: FDA Emergency Use Authorization 094 to Eli Lilly for bamlanivimab and estesevimab monoclonal antibody cocktail. https://www.fda.gov/media/145801/download

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On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). [1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On February 9, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. They are both investigational drugs and are not currently approved for any indication.

[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020.

[2] U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).

On February 25, 2021, FDA reissued the February 9, 2021 letter.[3] On August 27, 2021, FDA reissued the February 25, 2021 letter.[4]

On September 16, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 27, 2021 letter in its entirety, to also authorize bamlanivimab and etesevimab administered together for emergency use as post-exposure prophylaxis in certain adults and pediatric individuals.

Based on the review of the data from the Phase 2/3 BLAZE-1 trial (NCT04427501), a randomized, double-blind, placebo-controlled clinical trial, and the Phase 2 BLAZE-4 trial (NCT04634409), a randomized, double-blind, placebo-controlled clinical trial, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of bamlanivimab and etesevimab administered together outweigh the known and potential risks of such products.

Additionally, based on the review of the topline analysis of data from BLAZE-2 Part 1 (also known as Trial J2X-MC-PYAD; NCT04497987), a Phase 3 randomized, double-blind, placebocontrolled trial evaluating bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who

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are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under such conditions, the known and potential benefits of bamlanivimab and etesevimab outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of bamlanivimab and etesevimab administered together for treatment and as post-exposure prophylaxis of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

[3] FDA revised the condition on instructional and educational materials. New conditions were also incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized bamlanivimab and etesevimab against any global SARS-CoV-2 variant(s) of interest.

[4] FDA revised the authorized use for bamlanivimab and etesevimab administered together clarifying the meaning of "severe COVID-19" and further limited the use of bamlanivimab and etesevimab by authorizing bamlanivimab and etesevimab administered together only in those states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%. Revisions were also incorporated to the conditions on compliance with cGMPs, product quality reporting, requests for CMC (chemistry, manufacturing and controls) changes to this authorization, the provision of samples of the authorized bamlanivimab and etesevimab to HHS, upon request, and the conditions on advertising and promotion.

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>
> Remdesivir demonstrated an 87% reduction in risk for COVID-19-related hospitalization or death compared with the placebo group.
>
> "These latest data show remdesivir's potential to help high-risk patients recover before they get sicker and stay out of the hospital altogether," cardiologist Robert L. Gottlieb, of Baylor University Medical Center in Houston, said in the press release. Gottleib was the lead investigator for the study.

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> Compared to placebo (n=842), people who received a single dose of REGEN-COV (n=841) experienced:
>
> - 81.6% reduced risk of developing COVID-19 during the pre-specified follow-up period, between months 2-8 (7 REGEN-COV, 38 placebo; 95% confidence interval [CI]: 59.8%, 91.6%; nominal p<0.0001).

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- 81.5% reduced risk of developing COVID-19 at any time during the 8 months after receiving REGEN-COV (20 REGEN-COV, 108 placebo; 95% CI: 70.6%,88.4%; nominal p<0.0001).
- During the 8-month assessment period, 0 individuals in the REGEN-COV group were hospitalized due to COVID-19, compared to 6 individuals in the placebo group (1 person in the first month; 5 people during months 2-8). There were no deaths due to COVID-19 in any treatment group during the 8-month assessment period, and there were no new safety signals identified for REGEN-COV.

1012) 2021-11-08 Roche Investor Relations, Dr. Karl Mahler and Jon Kaspar Bayard: Investor Update: New Phase 3 analyses show that a single dose of REGEN-COV (casirivimab and imdevimab) provides long-term protection against COVID-19. https://www.roche.com/investors/updates/inv-update-2021-11-08.htm

1013) 2021-11-09 FDA: Template for developers of molecular and antigen diagnostic COVID-19 tests for home use. [Molecular and Antigen Home Use Test Template – US Food … and Supplemental template for Molecular and Antigen Diagnostic … that are downloadable at https://www.google.com/search?q=Template+for+developers+of+molecular+and+antigen+diagnostic+COVID-19+tests+for+home+use&oq=Template+for+developers+of+molecular+and+antigen+diagnostic+COVID-19+tests+for+home+use&aqs=chrome..69i57.1262j0j15&sourceid=chrome&ie=UTF-8].

1014) 2021-11-11 Armitage H: COVID-19 nasal spray vaccine in the works at Stanford Medicine. https://med.stanford.edu/news/all-news/2021/11/effort-to-develop-covid-vaccine-nasal-spray.html

1015) 2021-11-12 Diamond D: Messonier, Birx detail political interference in last year's coronavirus response. The Washington Post. https://www.washingtonpost.com/health/2021/11/12/messonnier-birx-coronavirus-response-interference/

1016) 2021-11-16 Linton C, Navarro A: Wyoming GOP votes to no longer recognize Liz Cheney. https://www.cbsnews.com/news/liz-cheney-wyoming-republican-party-recognize/ In this news report, it mentions that Kayleigh McEnany was given a subpoena to testify by the House select committee investigating the January 6 attack on the Capitol.

1017) 2021-11-17 Tin A: Pfizer asks FDA to grant emergency authorization for its COVID-19 pill. CBS News November 17, 2021. https://www.cbsnews.com/news/covid-pill-pfizer-seeks-fda-authorization/

1018) 2021-11-17 O'Keefe E, Brown K: U.S. bishops approve Communion guidelines after debate on Biden's eligibility. CBS NEWS. https://www.cbsnews.com/news/catholic-bishops-vote-biden-pelosi-communion-abortion-rights/

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1019) 2021-11-17 O'Shaughnessy JA: Regeneron Pharmaceuticals, Inc. EUA 091 regarding REGEN-COV. https://www.fda.gov/media/145610/download

1020) 2021-11-18 Picchi A: OSHA is suspending enforcement of the government's new employer vaccine rule. CBS News https://www.cbsnews.com/news/covid-vaccine-mandate-osha-suspending-enforcement/

1021) 2021-11-18 Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL, Hebner CM, Sager J, Mogailian E, Tipple C, Peppercorn A, Alexander E, Pag PS, Free A, Brinson C, Aldinger M, Shapiro AE, for the COMET-ICE Investigators: Early treatment for Covid-19 with SARS-Cov-2 neutralizing antibody Sotrovimab. N Engl J Med 2021 Nov 18; 385 (21): 1941-1950. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2107934?articleTools=true

1022) 2021-11-18 Korley FK, Durkalski-Mauldin V, Yeatts SD, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswall S, Kaplan A, Lowell E, Mcdyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLM, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit R, Barsa W, Callaway CW, for the SIREN-C3PO Investigators: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

> The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:
>
> > The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include **NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O.** In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and **NOT** by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

> Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960. https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the

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Supplementary Appendix which is very important can be found at (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf).

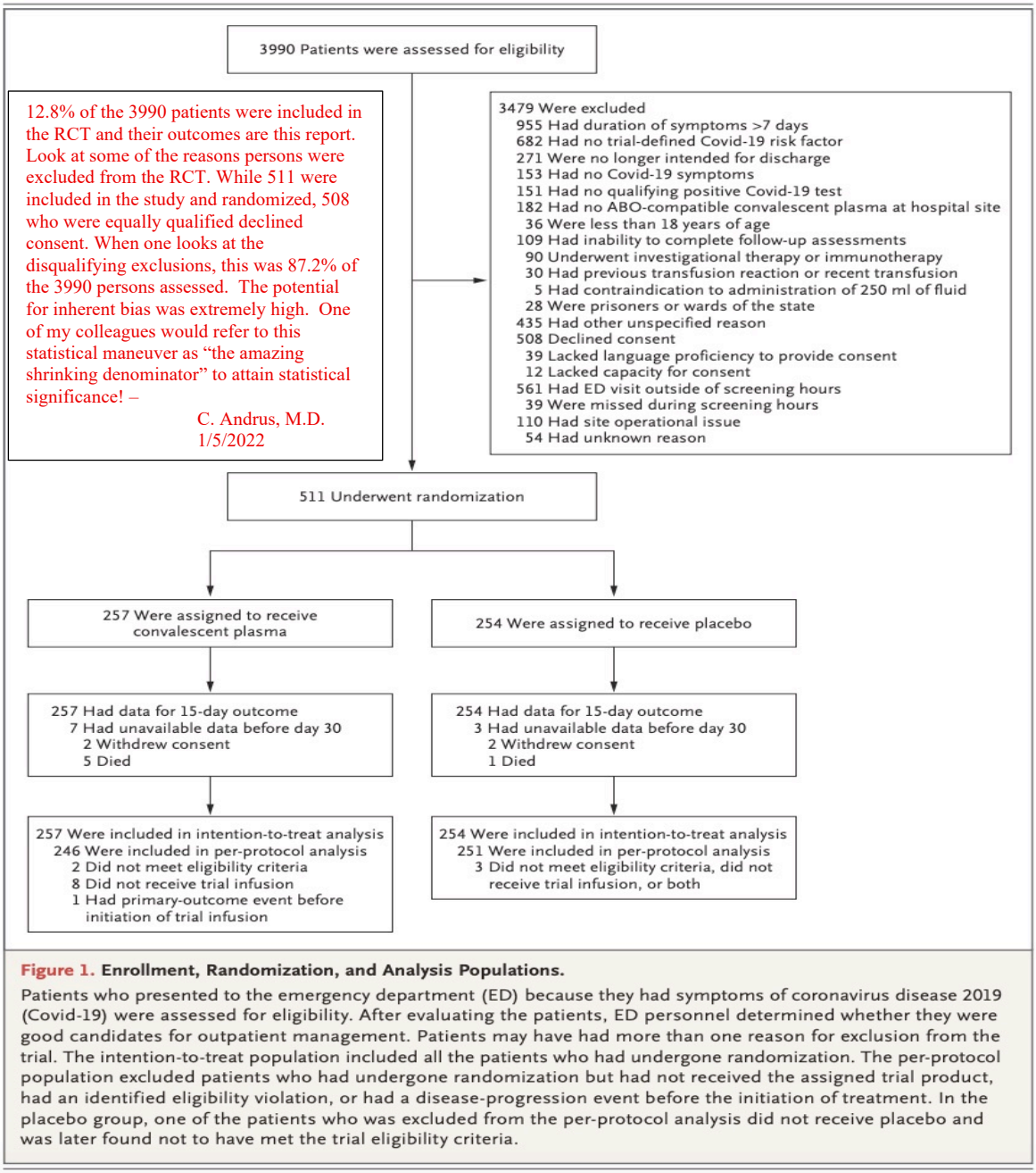
3990 Patients were assessed for eligibility
12.8% of the 3990 patients were included in the RCT and their outcomes are this report. Look at some of the reasons persons were excluded from the RCT. While 511 were included in the study and randomized, 508 who were equally qualified declined consent. When one looks at the disqualifying exclusions, this was 87.2% of the 3990 persons assessed. The potential for inherent bias was extremely high. One of my colleagues would refer to this statistical maneuver as "the amazing shrinking denominator" to attain statistical significance! –
C. Andrus, M.D.
1/5/2022
3479 Were excluded
955 Had duration of symptoms >7 days
682 Had no trial-defined Covid-19 risk factor
271 Were no longer intended for discharge
153 Had no Covid-19 symptoms
151 Had no qualifying positive Covid-19 test
182 Had no ABO-compatible convalescent plasma at hospital site
36 Were less than 18 years of age
109 Had inability to complete follow-up assessments
90 Underwent investigational therapy or immunotherapy
30 Had previous transfusion reaction or recent transfusion
5 Had contraindication to administration of 250 ml of fluid
28 Were prisoners or wards of the state
435 Had other unspecified reason
508 Declined consent
39 Lacked language proficiency to provide consent
12 Lacked capacity for consent
561 Had ED visit outside of screening hours
39 Were missed during screening hours
110 Had site operational issue
54 Had unknown reason
511 Underwent randomization
257 Were assigned to receive convalescent plasma
254 Were assigned to receive placebo
257 Had data for 15-day outcome
7 Had unavailable data before day 30
2 Withdrew consent
5 Died
254 Had data for 15-day outcome
3 Had unavailable data before day 30
2 Withdrew consent
1 Died
257 Were included in intention-to-treat analysis
246 Were included in per-protocol analysis
2 Did not meet eligibility criteria
8 Did not receive trial infusion
1 Had primary-outcome event before initiation of trial infusion
254 Were included in intention-to-treat analysis
251 Were included in per-protocol analysis
3 Did not meet eligibility criteria, did not receive trial infusion, or both

Figure 1. Enrollment, Randomization, and Analysis Populations.
Patients who presented to the emergency department (ED) because they had symptoms of coronavirus disease 2019 (Covid-19) were assessed for eligibility. After evaluating the patients, ED personnel determined whether they were good candidates for outpatient management. Patients may have had more than one reason for exclusion from the trial. The intention-to-treat population included all the patients who had undergone randomization. The per-protocol population excluded patients who had undergone randomization but had not received the assigned trial product, had an identified eligibility violation, or had a disease-progression event before the initiation of treatment. In the placebo group, one of the patients who was excluded from the per-protocol analysis did not receive placebo and was later found not to have met the trial eligibility criteria.

In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate

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in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum ß that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: …for the SIREN-C3PO Investigators* where the "*" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

> Has at least one study defined risk factor for severe COVID-19 illness:
>
> Age ≥ 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. **Characteristics of the Patients at Baseline**:

Characteristic	**Convalescent Plasma (N=257)**	**Placebo (N=254)**
Median age (IQR)	54 (42-62)	54 (40-62)

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participattion in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes?

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Prevention: *Active Immunization*: Vaccines

1023) 2021-11-18 CBS Interactive Inc.: Frozen vials marked "Smallpox" found in lab freezer in Pennsylvania, CDC says. https://www.cbsnews.com/news/smallpox-vials-lab-freezer-pennsylvania-cdc/

1024) 2021-11-18 Picchi A: OSHA is suspending enforcement of the government's new employer vaccine rule. https://www.cbsnews.com/news/covid-vaccine-mandate-osha-suspending-enforcement/

1025) 2021-11-18 Kimball S: Biden administration buys $10 million courses of Pfizer Covid treatment pill in $5 billion deal. https://www.cnbc.com/2021/11/18/biden-administration-buys-10-million-courses-of-pfizer-covid-treatment-pill.html

1026) 2021-11-19 Collin L: Upper Midwest faces spike in COVID-19 infections: "It's unprecedented." CBS Evening News, November 19, 2021. https://www.cbsnews.com/news/covid-19-upper-midwest-minnesota-spike/

1027) 2021-11-19 CBS News: U.S. Scientist says he's found the real COVID patient zero, and "strong evidence" pandemic started at animal market. CBS News, November 19, 2021. https://www.cbsnews.com/news/origin-covid-19-us-scientist-patient-zero-wuhan-china-evidence-market/

1028) 2021-11-19 FDA: FDA NEWS RELEASE: Coronavirus (COVID-19) Update: FDA expands eligibility for COVID-19 Vaccine boosters. November 19, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-covid-19-vaccine-boosters

1029) 2021-11-19 Tin A: CDC authorizes COVID vaccine boosters for all adults. CBS News, November 19, 2021. https://www.cbsnews.com/news/covid-vaccine-booster-shot-cdc-fda-authorization/

1030) 2021-11-21 The Tabernacle Choir at Temple Square: November 21, 2021 - #4810 Music & the Spoken Word. (This played on KMOX radio, St. Louis, MO at 6:00 a.m. while on my way to the St. Louis (John Cochran division) VAMC to round on the Veteran patients of General Surgery II. Listening to this message epitomized that of which the concept of gratitude of Thanksgiving Day is engendered and our assurance by the Constitution and the Bill of Rights of our freedoms of which we all-to-often take for granted.) https://www.thetabernaclechoir.org/videos/november-21-2021-4810-music-and-the-spoken-word.html

1031) 2021-11-21 Fauci A: Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response, CBS News. (Attempt of accessing this website on Google: Fauci Brennan *Face the Nation* on November 22, 2021 was unsuccessful but "autopsy"

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provided by yahoo): https://www.yahoo.com/now/fauci-says-hed-astounded-wasnt-150638991.html

> Margaret Brennan: Why aren't we having a national conversation about what went wrong? I mean, apart from this room right now, why isn't there a 9/11-type commission?
>
> Anthony Fauci, M.D.: Yeah. I think what's going to happen is that you are going to see that for sure, Margaret. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through—with already 760,000 Americans dying, and 40 plus million, at least, being infected. Close to 6 million people globally dying—and we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out [AUDIO OUT]..

WHEN the Wayback Machine (Internet Archive) was accessed November 22, 2021 of the only capture for the Yahoo version of Face the Nation of Nov 21, 2021: https://web.archive.org/web/20211121161530/https://www.yahoo.com/now/fauci-says-hed-astounded-wasnt-150638991.html yielded:

yahoo!

CBS News: Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response" Sun, November 21, 2021, 4:06 PM –Dr. Anthony Fauci tells Margaret Brennan in a wide-ranging conversation that he expects a full investigation into what went wrong in the Coronavirus response.

BUT THE ACTUAL INTERVIEW CANNOT BE OPENED stating: Cannot Play Video—Due to license restrictions; this video can only be viewed on Yahoo. RS-100-204.

WHEN on November 23, 2021, the Google attempt at searching: "Fauci Brennan Face the Nation" failed, searching for "Fauci Brennan Sixty Minutes" yielded the official CBS News website:

> https://www.cbsnews.com/video/fauci-says-hed-be-astounded-if-there-wasnt-an-autopsy-on-what-went-wrong-in-covid-response/#x

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Margaret Brennan: It's been almost two years since a mysterious virus began circulating in Wuhan, China. And there are still far more questions than answers about where it came from and how we can prepare for the next pandemic. For our broadcast Sunday we talked with Dr. Anthony Fauci to get his thoughts on just some of those questions. Here's a preview:

Margaret Brennan: Why aren't we having a national conversation about what went wrong? I mean, apart from this room right now, why isn't there a 9/11-type commission?

Anthony Fauci, M.D.: Yeah. I think what's going to happen is that you are going to see that for sure, Margaret. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through—with already 760,000 Americans dying, and 40 plus million, at least, being infected. **Close to 6 million people globally dying—and we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out.**

Margaret Brennan: Dr. Anthony Fauci coming up Sunday on Face the Nation.

When the web.archive using the official CBS New URL site above, Margaret Brennan video appears speaking without sound and when the arrow is the screen becomes black with a white circle spiraling in the center. The caption underneath reads: Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response. Dr. Anthony Fauci tells Margaret Brennan in a wide-ranging conversation that he expects a full investigation into what went wrong in the Coronavirus response.
https://web.archive.org/web/20211121152005/https://www.cbsnews.com/video/fauci-says-hed-be-astounded-if-there-wasnt-an-autopsy-on-what-went-wrong-in-covid-response/

1032) 2021-11-19 KFF-Henry J Kaiser Family Foundation: Status of State Medicaid Expansion Decisions: Interactive Map. https://www.kff.org/medicaid/issue-brief/status-of-state-medicaid-expansion-decisions-interactive-map/

1033) 2021-11-19, last updated: Boston National Historical Park: Smallpox, Inoculation, and the Revolutionary War. https://www.nps.gov/articles/000/smallpox-inoculation-revolutionary-war.htm

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1034) 2021-11-23 Trump D, Jr: @DonaldJTrumpJr https://twitter.com/DonaldJTrumpJr/status/1463366937065390085/photo/1

https://web.archive.org/web/20211124215038/https://twitter.com/DonaldJTrumpJr/status/1463366937065390085/photo/1

1035) 2021-11-23 CBS News: Full transcript of "Face the Nation" on November 21, 2021. "On this "Face the Nation" broadcast moderated by Margaret Brenna:" **The transcript has yet to be released but nowhere in the titles is Dr. Anthony Fauci listed.**

Sen. Kirsten Gillibrand, (D-NY)

Sen. Ted Cruz, (R-TX)

Derrick Johnson, President and CEO, NAACP

Dr. Scott Gottlieb, Former FDA Commissioner

Anthony Salvanto, CBS News Elections & Surveys Director

https://web.archive.org/web/20211121192431/https://www.cbsnews.com/news/full-transcript-of-face-the-nation-on-november-21-2021/

https://www.cbsnews.com/news/full-transcript-of-face-the-nation-on-november-21-2021/

1036) 2021-11-28 Fauci A, Brennan M: Transcript: Dr. Anthony Fauci on "Face the Nation," November 28, 2021. CBS NEWS, Face the Nation, 2021 November 28, 2021, 7:21 AM https://www.cbsnews.com/news/transcript-dr-anthony-fauci-on-face-the-nation-november-28-2021/

Please note that the statement regarding autopsy was edited out from the discussion that aired on Sunday morning Face the Nation on November 28, 2021 on the St. Louis affiliate KMOV:

DR. FAUCI: Yeah, I think what's going to happen is that you are going to see that for sure, MARGARET. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through with already 760,000 Americans dying and 40 plus million at least being infected, close to six million people globally dying. **And we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out.** So people should not think that that's not going to happen. It's not happening now because everybody's focusing on getting this thing under control.

1037) 2021-11-28 Bice A: Fauci: 'I'm going to be saving lives and they're going to be lying.' POLITICO https://www.politico.com/news/2021/11/28/fauci-lying-covid-research-cruz-523412

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Prevention: *Active Immunization*: Vaccines

1038) 2021-11-29 Kimball S: Pfizer CEO confident Covid treatment pill will be effective against omicron variant. https://www.cnbc.com/2021/11/29/pfizer-ceo-confident-covid-treatment-pill-effective-against-omicron-variant.html

1039) 2021-12 Personalis, Inc.: Veterans Health Administration 75 Years: *A legacy of service. The future of care.* Personalis, Inc., 1330 O'Brien Drive, Menlo Park, CA. 94025. www.personalis.com wrightusa.com, page 20.

1040) 2021-12-01 Lederer EM: Fauci says COVID diverted resources from fighting AIDS. https://www.aol.com/news/fauci-says-covid-diverted-resources-035825200-153355420.html

1041) 2021-12-02. Weinrech DM and Others: *e*81 REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. D.M. Weinreich and Others.

2021-09-29 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Xiao J, Hooper AT, Hamilton JD, Musser BJ, Rofail D, Hussein M, Im J, Atmodjo DY, Perry C, Pan C, Mahmood A, Hosain R, Davis JD, Turner KC, Baum A, Kyratsous CA, Kim Y, Kampman W, Roque-Guerrero L, Acloque G, Aazami H, Cannon K, Simon-Campos, Bocchini JA, Kowal B, DiCioccio AT, Soo Y, Geba GP, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, for the Trial Investigators*: REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med posted on NEJM.org on September 29, 2021. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2108163?articleTools=true with the "*" which is the complete article: https://www.nejm.org/doi/full/10.1056/NEJMoa2108163 of September 29, 2021.

On the hardcopy version of this paper is noted in the front page index of *The New England Journal of Medicine*, 2021 December 2; 385 (23), front page INDEX:

*e*81 REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. D.M. Weinreich and Others but the article is not in this hardcopy but in the electronic format only: https://www.nejm.org/doi/full/10.1056/NEJMoa2108163 and for the entire supplement: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2108163/suppl_file/nejmoa2108163_appendix.pdf

1042) 2021-12-02 Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD, Kornowski R: Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med 2021 December 2; 385 (23): 2132-2139. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110737?articleTools=true

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Prevention: *Active Immunization*: Vaccines

https://www.nejm.org/doi/full/10.1056/NEJMoa2110737 which is the electronic version published on October 6, 2021.

1043) 2021-12-02 Mevorach D, Anis E, Cedar N, Bromberg M, Nadir E, Olsha-Castell S, Arad D, Hasin T. Levi N, Amir O, Meir K, Cohen D, Dichtiar R, Novick D, Hershkovitz Y, Dagan R, Leitersdorf I, Ben-Ami R, Miskin I, Saliba W, Muhsen K, Levi Y, Green MS, Keinan-Boker L, Alroy-Preis S: Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Isreal. N Engl J Med 2021 December 2; 385 (23): 2140-2149. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2109730

1044) 2021-12-02 Caforio ALP: Receipt of mRNA Vaccine against Covid-19 and myocarditis. N Engl J Med 2021 December 2; 385 (23): 2189-2190. https://www.nejm.org/doi/pdf/10.1056/NEJMe2116493?articleTools=true

1045) 2021-12-02 Chutel L, Pénza-Peña R: Prior infection is little defense against virus variant, scientists say. Evidence from South Africa, where the Omicron variant already dominates, shows a high rate of reinfection of people who have already had the coronavirus. The New York Times https://www.nytimes.com/2021/12/02/world/africa/virus-omicron-variant-reinfection.html

1046) 2021-12-03 Albert V, Tin A: Omicron COVID-19 variant detected in 5 states, a day after first case was reported in U.S. CBS News https://www.cbsnews.com/news/omicron-variant-covid-19-cases-detected-united-states/

1047) 2021-12-03 FDA: FDA expands authorization of two monoclonal antibodies for treatment and post-exposure prevention of COVID-19 to younger pediatric patients, including newborns. U.S. Food and Drug Administration News Release. https://www.fda.gov/news-events/press-announcements/fda-expands-authorization-two-monoclonal-antibodies-treatment-and-post-exposure-prevention-covid-19

PLEASE NOTE:

Mr. President, the actual EUA regarding this FDA News Release was based on the EUA letter by RADM Denise M. Hinton, R.N., M.S., F.D.A. Chief Scientist, on September 16, 2021. Mr. President, over the last 18 months, RADM Hinton has issued FDA EUAs regarding *Passive Immunization agents* like COVID-19 Convalescent Plasma; Monoclonal Antibodies and Antibody Cocktails, etc.—because that is her job. She has walked the straight and narrow in responsibly issuing these EUAs for the last 18 months for that is her job; and she has done it admirably! In those introductory discussions of each of the EUAs she has laid out the evolutionary histories of these drugs and biologic agents and the justifications and directions on how to clinically administer them. Unfortunately, every EUA continues the status of the drug or biologic as *Investigational (Experimental).* What does that mean? – It means that clinically a physician has to apply for an

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individual FDA *Investigational New Drug (IND)* application every time he/she has a patient who has contracted COVID-19 and administration of the drug or biologic is indicated.

The FDA tried to circumvent the need for individual physicians requesting individual INDs for individual patients regarding COVID-19 Convalescent Plasma from March 24, 2020 until August 23, 2020 by issuing an Expanded Access authorization. An expanded access authorization is by FDA/NIH definition "compassionate" use – providing an *Investigational Drug* given off protocol with the stipulation that any outcome data cannot be used to generate any prospective research information.

1048) 2021-12-03 Lilly: Lilly's bamlanivimab with etesevimab authorized as the first and only neutralizing antibody for emergency use in COVID-19 patients under the age of 12. https://investor.lilly.com/node/46306/pdf

1049) 2021-12-03 Enago Academy: Quick guide to biostatistics in clinical research: Hypothesis testing. https://www.enago.com/academy/quick-guide-to-biostatistics-in-clinical-research-hypothesis-testing/

2021-01-22 Enago Academy: A quick guide to clinical trials (Part 1: An Overview). https://www.enago.com/academy/a-quick-guide-to-clinical-trials-part-1-an-overview/

2018-05-23 Enago Academy: A quick guide to clinical trials (Part 2: The Process). https://www.enago.com/academy/a-quick-guide-to-clinical-trials-part-2-the-process/

1050) 2021-12-06 wcg FDANEWS: FDA updates EUA for Eli Lilly's COVID-19 antibody cocktail to include young children. https://www.fdanews.com/articles/205656-fda-updates-eua-for-eli-lillys-covid-19-antibody-cocktail-to-include-young-children

1051) 2021-12-07 World Health Organization: WHO recommends against the use of convalescent plasma to treat COVID-19. December 7, 2021. https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-of-convalescent-plasma-to-treat-covid-19#:~:text=Convalescent%20plasma%20is%20a%20transfusion,while%20it%20has%20significant%20costs

1052) 2021-12-08 Kimball S: Pfizer will submit full data on Covid treatment pill to the FDA in a few days, CEO says. CNBC PRO Dec 8, 20212. https://www.cnbc.com/2021/12/08/pfizer-will-submit-full-data-on-covid-treatment-pill-to-the-fda-in-a-few-days-ceo-says.html

1053) 2021-12-08 FDA News Release: Coronavirus (COVID-19) Update: FDA authorizes new long-acting monoclonal antibodies for pre-exposure prevention of COVID-19 in certain individuals. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-

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update-fda-authorizes-new-long-acting-monoclonal-antibodies-pre-exposure#:~:text=Today%2C%20the%20U.S.%20Food%20and,years%20of%20age%20and%20older Per an e-mail of February 18, 2022, 1:31 PM from the Deputy Chief of Staff—John Cochran Division, VA St. Louis Health Care System: The St. Louis VA has received a very limited supply of Evusheld for initial distribution. The Scarce Resource Team has planned an allocation method to maximize the ethical principles of respect, consistency, stewardship, transparency, and equity.

1054) 2021-12-08 Jimenez D: Covid-19: GSK's sotrovimab retains activity against Omicron variant. Pharmaceutical Technology. https://www.pharmaceutical-technology.com/special-focus/covid-19/covid-19-gsk-sotrovimab-activity-omicron-variant/#:~:text=GlaxoSmithKline%20(GSK)%20and%20Vir%20Biotechnology,%2DCoV%2D2%20variant%20Omicron.

1055) 2021-12-08 NIH / NIAID: COVID-19 single-dose nasal vaccine designed for infants, children. https://www.niaid.nih.gov/news-events/covid-19-single-dose-nasal-vaccine

1056) 2021-12-13 Supreme Court of the U.S.: JOSEPH R. BIDEN, Jr, PRESIDENT OF THE UNITED STATES, et al., APPLICANTS 21A240 v. MISSOURI, et al. and XAVIER BECERRA, SECRETARY OF HEALTH AND HUMAN SERVICES, et al APPLICANTS 21A241 v. LOUISANA, et al. on applications for stays. https://www.supremecourt.gov/opinions/21pdf/21a240_d18e.pdf

1057) 2021-12-16 AstraZeneca: EVUSHELD long-acting antibody combination retains neutralizing activity antibody combination retains neutralizing activity against Omicron variant in independent FDA study. https://www.astrazeneca-us.com/media/press-releases/2021/evusheld-long-acting-antibody-combination-retains-neutralizing-activity-against-omicron-variant-in-independent-fda-study.html

1058) 2021-12-16 NIH: COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

1059) 2021-12-16 NIH: Anti-SARS-CoV-2 Monoclonal Antibodies. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

1060) 2021-12-16 NIH: Anti-SARS-CoV-2 Monoclonal Antibodies, Table A. (Last updated 16, 2021) https://www.covid19treatmentguidelines.nih.gov/tables/table-a/ According to the Wayback Machine there are digital copies of updates going back to August 6, 2021 with the NIH "last update" is August 4, 2021. https://web.archive.org/web/20210806205833/https://www.covid19treatmentguidelines.nih.gov/tables/table-a/

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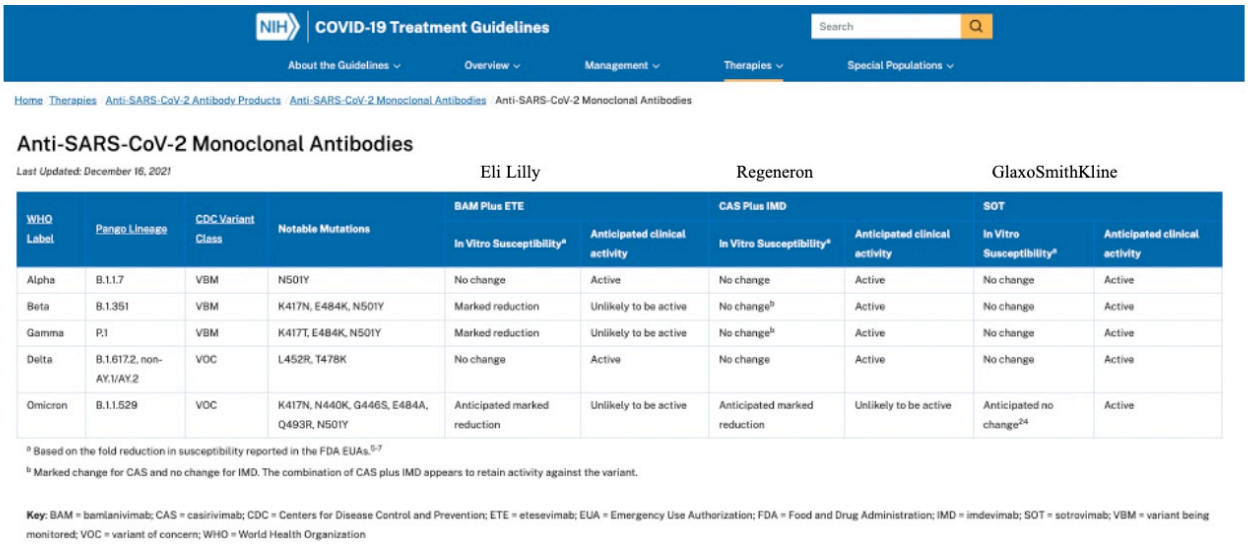

NIH COVID-19 Treatment Guidelines

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Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: December 16, 2021

Eli Lilly Regeneron GlaxoSmithKline

WHO Label	Pango Lineage	CDC Variant Class	Notable Mutations	BAM Plus ETE		CAS Plus IMD		SOT	
				In Vitro Susceptibility[a]	Anticipated clinical activity	In Vitro Susceptibility[a]	Anticipated clinical activity	In Vitro Susceptibility[a]	Anticipated clinical activity
Alpha	B.1.1.7	VBM	N501Y	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VBM	K417N, E484K, N501Y	Marked reduction	Unlikely to be active	No change[b]	Active	No change	Active
Gamma	P.1	VBM	K417T, E484K, N501Y	Marked reduction	Unlikely to be active	No change[b]	Active	No change	Active
Delta	B.1.617.2, non-AY.1/AY.2	VOC	L452R, T478K	No change	Active	No change	Active	No change	Active
Omicron	B.1.1.529	VOC	K417N, N440K, G446S, E484A, Q493R, N501Y	Anticipated marked reduction	Unlikely to be active	Anticipated marked reduction	Unlikely to be active	Anticipated no change[24]	Active

[a] Based on the fold reduction in susceptibility reported in the FDA EUAs.[5-7]

[b] Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

Key: BAM = bamlanivimab; CAS = casirivimab; CDC = Centers for Disease Control and Prevention; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; SOT = sotrovimab; VBM = variant being monitored; VOC = variant of concern; WHO = World Health Organization

1061) 2021-12-16 CDC: CDC endorses ACIP's updated COVID-19 vaccine recommendations. https://www.cdc.gov/media/releases/2021/s1216-covid-19-vaccines.html

> Today, CDC is endorsing updated recommendations made by the Advisory Committee on Immunization Practices (ACIP) for the prevention of COVID-19, expressing a clinical preference for individuals to receive an mRNA COVID-19 vaccine over Johnson & Johnson's COVID-19 vaccine. ACIP's unanimous recommendation followed a robust discussion of the latest evidence on vaccine effectiveness, vaccine safety and rare adverse events, and consideration of the U.S. vaccine supply. The U.S. supply of mRNA vaccines is abundant – with nearly 100 million doses in the field for immediate use. This updated CDC recommendation follows similar recommendations from other countries, including Canada and the United Kingdom. Given the current state of the pandemic both here and around the world, the ACIP reaffirmed that receiving any vaccine is better than being unvaccinated. Individuals who are unable or unwilling to receive an mRNA vaccine will continue to have access to Johnson & Johnson's COVID-19 vaccine.

1062) 2021-12-17 Cooper R: Noble lies are a public health hazard. THE WEEK, 17 Dec 2021. https://theweek.com/coronavirus/1008155/noble-lies-are-a-public-health-hazard

1063) 2021-12-19 LaPook J: COVID and safer holiday gatherings, 11:10 -14:57 https://www.cbs.com/shows/cbs-sunday-morning/video/ztOo3TeLHgxraEUXbeOmcDfzIn7BYZCX/-sunday-morning-full-episode-12-19/

1064) 2021-12-19 Braver R: Dr. Francis Collins retires as NIH Director, 15:01 – 22:38, CBS News https://www.cbsnews.com/video/retiring-nih-director-dr-francis-collins/

1065) 2021-12-19 Collins F: Transcript: NIH Director Dr. Francis Collins on "Face the Nation," December 19, 2021. CBSNews https://www.cbsnews.com/news/transcript-nih-director-dr-francis-collins-face-the-nation-12-19-2021/

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1066) 2021-12-19 Dellatto M: Fauci: Pfizer's possibly game-changing Covid-19 pill won't be widely available for 'months." https://www.forbes.com/sites/marisadellatto/2021/12/19/fauci-pfizers-possibly-game-changing-covid-19-pill-wont-be-widely-available-for-months/?sh=1bc7e423cc30

1067) 2021-12-20 Senefeld JW, Johnson PW, Kunze KL, Bloch EM, van Helmond N, Golafshar MA, Klassen SA, Klompas AM, Sexton MA, Diaz Soto JC, Grossman BJ, Tobian AAR, Goel R, Wiggins CC, Bruno KA, van Buskirk CM, Stubbs JR, Petersen MM, Sachais BS, Buras MS, Wieczorek MA, Russoniello B, Dumont LJ, Baker SE, Vassallo RR, Shepherd JRA, Young PP, Verdun NC, Marks P, Haley NR, Katz L, Herasevich V, Waxman DA, Whelan ER, Bergman A, Clayburn AJ, Grabowski MK, Larson KF, Ripoll JG, Andersen KJ, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Blair JE, Buchholtz ZA, Pletsch MC, Wright K, Greenshields JT, Joyner MJ, Wright RS, Carter RE, Fairweather DL: Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study. PLOS Medicine 2021 December 20; 1-28. https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003872

1068) 2021-12-20 O'Shaunghnessy JA: FDA EUA regarding AstraZemeca Pharmaceuticals LP's EVUSHELD for use as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals… Tixagevimab and Cilgavimab, the active components of EVUSHELD, are neutralizing IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. EVUSHELD is an investigational drug and is not approved for any uses, including use as pre-exposure prophylaxis of COVID-19. https://www.fda.gov/media/154704/download

1069) 2021-12-21 Kozlov M: Omicron overpowers key COVID antibody treatments in early tests—Nearly all of the monoclonal antibodies used to prevent severe disease fail to stand up to the new variant, laboratory assays show. https://www.nature.com/articles/d41586-021-03829-0

1070) 2021-12-21 Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, Mosnaim GS, Gniadek TJ, Fukuta Y, Patel B, Heath SL, Levine AC, Meisenberg BR, Spivak ES, Anjan S, Huaman MA, Blair JE, Currier JS, Paxton JH, Gerber JM, Petrini JR, Broderick PB, Rausch W, Cordisco ME, Hammel J, Greenblatt B, Cluzet VC, Cruser D, Oei K, Abinante M, Hammitt LL, Sutcliffe CG, Forthal DN, Zand MS, Cachay ER, Raval JS, Kassaye SG, Foster EC, Roth M, Marshall CE, Yarava A, Lane K, McBee NA, Gawad AL, Karlen N, Singh A, Ford DE, Jabs DA, Appel LJ, Shade DM, Ehrhardt S, Baksh SN, Laeyendecker O, Pekosz A, Klein SL, Casadevall A, Tobian AAR, Hanley DF: Randomized controlled trial of early outpatient COVID-19 treatment with high-titer. https://www.medrxiv.org/content/10.1101/2021.12.10.21267485v1.full.pdf

1071) 2021-12-22 FDA: Coronavirus (COVID-19) Update: FDA authorizes first oral antiviral for treatment of COVID-19. https://www.fda.gov/news-events/press-

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announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19

1072) 2021-12-22 O'Shaughnessy JA, acting FDA Chief Scientist: To Eli Lilly and Company. RE: Emergency Use Authorization 094. U.S. Food and Drug Administration. https://web.archive.org/web/20211224034648/https://www.fda.gov/media/145801/download

> On December 22, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 3, 2021 letter in its entirety, to remove the limitation on the authorized use of bamlanivimab and etesevimab that previously authorized bamlanivimab and etesevimab administered together only in those states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%. FDA is also revising the healthcare provider fact sheet to remove this limitation on the authorized use of bamlanivimab and etesevimab and to incorporate additional virology information.

https://www.fda.gov/media/145801/download January 24, 2022.

https://www.fda.gov/media/156151/download February 11, 2022

https://www.fda.gov/media/143602/download Revoked March 2, 2021

2022-05-04 ASPR Office of the Assistant Secretary for Preparedness & Response: Important Bamlanivimab/Etesevimab Updates. https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Bamlanivimab-etesevimab/Pages/default.aspx

1073) 2021-12-22 Kavanaugh: Miscellaneous Order (12/22/2021) for oral arguments before the U.S. Supreme Court on Friday, January 7, 2022 in application 21A244: NAT. FED'N OF INDEP. BUS., ET AL. V. DEPT. OF LABOR, OSHA, ET AL. and application 21A247: OHIO, ET AL. V. DEPT. OF LABOR, ET AL. https://www.supremecourt.gov/orders/courtorders/122221zr2_f20h.pdf

1074) 2021-12-22 Barnes R: Supreme Court sets special hearing for Biden's vaccine rules for health-care workers, private businesses. The Washington Post. https://www.washingtonpost.com/politics/courts_law/biden-vaccine-mandates-supreme-court/2021/12/22/dd3bab94-6382-11ec-a7e8-3a8455b71fad_story.html

1075) 2021-12-22 Judith Dawson judith.dawson@bjc

> Subject: 12/22/21 COVID-19 Communications to Providers
>
> Being sent to active Medical Staff, Midlevel Providers and Office Managers:
>
> **mAB Clinic Updates:**
> **mAb Therapy Exceeding Capacity**: Demands for monoclonal antibody (mAb) therapy has exceeded capacity at BJC's clinics. To triage patients during these unprecedented volumes, orders will be limited to qualifying high-risk patients who have a positive COVID-19 test. We will cease

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accepting adult patients for post-exposure prophylaxis at this time. For information on eligibility and ordering, please visit. www.bjc.org/for-physicians/mab

Expanded EUA Criteria: Based on expanded EUA criteria, BJC HealthCare and Washington University are now able to offer monoclonal antibody therapy (mAb) to patients 0-11 years old. On Monday, December 20, 2021, St. Louis Children's Hospital began treating high-risk pediatric patients of all ages at the mAb clinic on the Washington University School of Medicine Campus as well as at the St. Louis Children's Specialty Care Center (CSCC) – South County. Please visit www.bjc.org/For-Physicians/mab for ordering information. …

1076) 2021-12-22 O'Shaughnessy: FDA: EUA 105 letter to Pfizer regarding PAXLOID [nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentration to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOID is not approved for any use, including treatment of COVID-19.] https://web.archive.org/web/20211222180424/https://www.fda.gov/media/155049/download

PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

https://www.fda.gov/media/155049/download (2022-04-14)

This letter is in response to Pfizer, Inc.'s (Pfizer) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3). On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). 1 On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.2 PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOVID is not approved for any use, including for use for the treatment of COVID-19. Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that

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PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing

[1]U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020. [2] U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).

at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product. Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of PAXLOVID for the treatment of mild-tomoderate COVID-19 in certain adults and pediatric patients, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

1077) 2021-12-22 Associated Press: Experts warn of 'perfect storm' in Missouri as cases jump. KSHB news. https://www.kshb.com/news/coronavirus/experts-warn-of-perfect-storm-in-missouri-as-cases-jump

1078) 2021-12-22 Gilead: Gilead announces New England Journal of Medicine publication of data demonstrating Veklury (Remdesivir) significantly reduced risk of hospitalization in high-risk patients with COVID-19. –Subgroup analyses show consistently high efficacy for patients regardless of underlying medical conditions associated with higher risk for severe COVID-19 compared with placebo-- https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/gilead-announces-new-england-journal-of-medicine-publication-of-data-demonstrating-veklury-remdesivir-significantly-reduced-risk-of-hospitalization

1079) 2021-12-23 Thomas K, Robbins R: Covid antibody drugs go unused as need soars. The New York Times. https://web.archive.org/web/20201223152514/https://www.nytimes.com/2020/12/23/health/covid-antibody-treatment.html

1080) 2021-12-23 Haseltine WA: Omicron evades most but fortunately not all monoclonal antibodies. Forbes Healthcare https://www.forbes.com/sites/williamhaseltine/2021/12/23/omicron-evades-most-but-fortunately-not-all-monoclonal-antibodies/?sh=fecdf6082fec

1081) 2021-12-23 O'Shaughnessy JA: EUA Letter 108 to Merck to authorize molnupiravir (a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis). https://web.archive.org/web/20211223145523/https://www.fda.gov/media/155053/download

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

1082) 2021-12-23. Tin A: FDA authorizes second COVID antiviral pill, from Merck, if no alternatives available. https://www.cbsnews.com/news/fda-authorizes-covid-antiviral-pill-merck-molnupiravir/#

1083) 2021-12-23 FDA: Coronavirus (COVID-19) Update: FDA Authorizes additional oral antiviral for treatment of COVID-19 in certain adults. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain

1084) 2021-12-23 Quinn M: Supreme Court to hear challenges to Biden COVID-19 vaccine rules for health care workers, large companies. CBS NEWS https://www.cbsnews.com/news/supreme-court-biden-covid-19-vaccine-rules-health-care-workers-large-companies/

1085) 2021-12-23 Ellis R: Monoclonal antibody for Omicron in short supply. WEBMD news brief. https://www.webmd.com/lung/news/20211222/monoclonal-antibody-for-omicron-in-short-supply

1086) 2021-12-23 Minnesota Department of Health: Ethical framework for allocation of Monoclonal Antibodies during the COVID-19 Pandemic. https://web.archive.org/web/20211224142017/https://www.health.state.mn.us/diseases/coronavirus/hcp/mabethical.pdf

This framework has been updated since 11/12/21 to clarify allocation priorities, clinical prioritization, potential for deprioritization of access for post-exposure prophylaxis (PEP) patients, and lottery considerations.

Introduction

Since November 2020, the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) to permit the emergency use of investigational monoclonal antibody (mAb) therapies for the treatment of mild to moderate COVID-19 in adult and pediatric patients. The currently authorized mAbs are:

- Casirivimab/imdevimab (Regeneron) EUA issued Nov. 21, 2020[1]
- Bamlanivimab/etesevimab (Eli Lilly) EUA issued Feb. 9, 2021[2]
- Sotrovimab (GlaxoSmithKline LLC) EUA issued Oct. 8, 2021[3]

The FDA issued an EUA on Nov. 9 for the use of bamlanivimab alone for treatment of COVID-19. 2020.[4] As of April 16, 2021; however, this EUA has been revoked.[5] This revocation was issued due to concerns about the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone, resulting in the increased risk for

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treatment failure. The FDA therefore determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use.

In May and June of 2021, the FDA issued updated eligibility criteria for mAb treatment for both casirivimab/imdevimab (Regeneron) and bamlanivimab/etesevimab, and authorized the addition of a subcutaneous route of administration for casirivimab/imdevimab (Regeneron) as an alternative when intravenous infusion is not feasible and would lead to delay in treatment.[6]

On July 30, 2021, the FDA updated the EUA for casirivimab/imdevimab (Regeneron) to authorize use of this product for post-exposure prophylaxis (PEP) in some patients.[7] On Sept. 16, 2021, the FDA updated the EUA for bamlanivimab/etesevimab to authorize use of this product for PEP in the same patient population as that for PEP using the Regeneron product, and with specific guidance that bamlanivimab/etesevimab would only be authorized for continued use in states where prevalent COVID-19 variants are susceptible to the mAb.[8]

With respect to treatment uses, the FDA has noted in the EUAs for the currently authorized mAbs:

"Based on the totality of scientific evidence available to FDA, it is reasonable to believe that … " these monoclonal antibody therapies " … may be effective in treating mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age or older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when used under the conditions described in this authorization, the known and potential benefits … when used to treat COVID-19 in such patients outweigh the known and potential risks of such product(s)."[9]

The patient eligibility criteria listed in the EUA for the authorization of each of the currently authorized monoclonal antibody therapies are identical. For that reason, this document covers each of these therapies under the umbrella term "mAb." Notably, these mAbs are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. The U.S. government has secured supplies of these investigational antibody therapies for distribution to states. Infusion facilities may order directly from the U.S. Department of Health and Human Services as needed.

Allocation and administration of these mAbs for treatment are **time-sensitive**, as the EUA for each specifies that infusions be administered as soon as possible after a positive COVID-19 test result and **within 10 days of symptom onset.**[10,11] Consequently, communicating to health care systems, physicians, patients, and COVID-19 test sites the importance of rapid testing and referral for potential infusion is crucial. The EUA Fact Sheet states: "For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment."[12]

For post-exposure prophylaxis (PEP) uses, the FDA notes:

"[I]t is reasonable to believe that [the authorized mAbs] may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under [such condition]s, the known and potential benefits of [the authorized mAbs] outweigh the known and potential risks of such products."[13]

Allocation and administration of mAbs for PEP are also time-sensitive. The EUA states that mAbs should be administered for PEP "as soon as possible following exposure to SARS-CoV-2," without providing a more specific timeframe.[11] **This framework recommends administering mAbs for PEP within 10 days from exposure for eligible patients who are not expected to mount an adequate immune response – e.g., those with immunocompromising conditions or on immunosuppressive medications – and administering mAbs for PEP within five days from exposure for all other eligible patients.** Thus, communicating to health care systems, physicians, and relevant groups of patients about the option of accessing mAbs for PEP is crucial. For PEP, mAbs may be administered either via infusion or subcutaneous injection.[12]

On Sept. 3, 2021, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel issued guidance outlining clinical prioritization when there is insufficient capacity to meet need for mAbs.[14] **MCEC recommends a somewhat different approach to allocation in scarcity, which is outlined below.** The NIH panel's guidance recommends prioritizing treatment uses of mAbs over all PEP. This MDH framework **prioritizes PEP for highly immunocompromised individuals** (as specified on Page 9) **along with treatment uses, over PEP for immunocompetent individuals,** for two reasons. First, highly immunocompromised individuals face extremely high risk of progression to severe COVID-19. Second, unlike immunocompetent individuals, immunocompromised patients who develop COVID-19 infection may progress to severe disease too quickly to reasonably allow them to access mAbs for treatment. Thus, to adequately protect this population, PEP for immunocompromised individuals should be managed differently than PEP for immunocompetent individuals. In addition, the NIH panel's guidance recommends prioritizing "unvaccinated or incompletely vaccinated individuals" over vaccinated ones in allocation of mAbs (as well as prioritizing vaccinated individuals who are immunocompromised). In allocating mAbs for treatment of COVID-positive patients, this MDH framework deviates from that guidance by permitting the **prioritization of both vaccinated and unvaccinated individuals who are at very high risk of progression to severe COVID-19**, even if they are not immunocompromised.

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This document provides ethical guidance regarding the allocation of mAbs. When the first mAb – bamlanivimab – was first made available through an EUA, it was anticipated that supply would be insufficient to meet need. The Minnesota Department of Health (MDH) and the Minnesota COVID-19 Ethics Collaborative (MCEC) developed Interim Ethical Guidance for Monoclonal Antibody Administration. That and subsequent versions of this guidance document are now superseded by this framework.

This document was developed by MDH working with a subgroup of the MCEC, including the co-leads, with additional clinical input, and was subsequently reviewed by MCEC. The document addresses relevant past guidance developed at MDH, key ethical values, and how allocation should occur both under conditions of scarcity and conditions of sufficient supply regarding: (1) allocation to hospitals and health systems throughout the state and (2) allocation among patients within each infusion or injection facility (which will initially be affiliated with hospitals).

MCEC recommends this ethical guidance be operationalized using a centralized system called the Minnesota Resource Access Platform (MNRAP). This centralized approach promotes consistency among institutions and systems across the state of Minnesota, which is ethically important because it:

- Enhances transparency and the trustworthiness of pandemic response throughout the state;
- Fosters a common standard of care and access, and so helps to ensure fairness; and
- Promotes equity in allocation for all Minnesotans, whether or not they are affiliated with a health system.

After adopting this framework in February 2021, and after requests from a small number of health care systems, MDH decided to permit some health systems to opt out of using MNRAP to allocate mAbs on the condition that these systems demonstrate that their allocation process meets the ethical requirements of this framework and is at least as fair and equitable as MNRAP. These conditions require that opted-out systems accept unaffiliated patients without disadvantaging them, and that they implement their own lottery process when their system is in scarcity, as defined either by insufficient doses or appointment slots to meet demand. The weighted lottery process should account for the same clinical and nonclinical factors as outlined in this guidance (refer to "Escalating approaches to scarce resource allocation" below for those specific requirements). Opted-out systems should also meet additional reporting requirements set by MDH to demonstrate their respective systems are performing as intended. **Given the current state of mAb supply, there is the possibility that mAbs may need to be rationed due to scarcity. Thus, all systems that have not opted out of MNRAP should use MNRAP for all mAbs allocation decisions, and not supplement MNRAP with allocation processes internal to their respective systems.** In other words, all patients for facilities that have not opted out of MNRAP should be run through the MNRAP system.

1087) 2021-12-27 The National Law Review: Will answers come in 2022? Supreme Court sets January 7 hearing on COVID Vaccine Mandates. https://www.natlawreview.com/article/will-answers-come-2022-supreme-court-sets-january-7-hearing-covid-vaccine-mandates

1088) 2021-12-27 CDC: CDC updates and shortens recommended isolation and quarantine period for general population. https://www.cdc.gov/media/releases/2021/s1227-isolation-quarantine-guidance.html

1089) 2021-12-28 Villapando N, Villalpando R: Texas runs out of monoclonal antibody treatment to fight omicron variant of COVID-19. USA TODAY https://www.usatoday.com/story/news/nation/2021/12/28/texas-runs-out-monoclonal-antibody-sotrovimab-treatment-fight-omicron-covid/9031897002/

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Prevention: *Active Immunization*: Vaccines

1090) 2021-12-28 Jacqueline A. O'Shaughnessy, Ph.D., Acting Chief Scientist, FDA, U.S. Food & Drug: Letter to Dawn O'Connell, Assistant Secretary for Preparedness and Response, Office of Assistant Secretary for Preparedness and Response, Office of the Secretary, U.S. Department of Health and Human Services: Most recent EUA Letter regarding COVID-19 Convalescent Plasma, **December 28, 2021**. https://www.fda.gov/media/141477/download

1091) 2021-12-29 Dorman JL: Former Surgeon General Jerome Adams says CDC officials wouldn't follow the new guidance 'for their own family.' INSIDER https://www.businessinsider.com/jerome-adams-criticizes-cdc-guidance-isolation-covid-19-antigen-tests-2021-12

1092) 2021-12-30 NIH COVID-19 Treatment Guidelines: The COVIDF-19 treatment guidelines panel's statement on therapies for high-risk, nonhospitalized patients with mild to moderated COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

1093) 2021-12-30 McCammon S, Doucleff M: Omicron causes record-breaking COVID cases in the U.S. and globally. NPR 2021 Dec. 30 https://www.npr.org/2021/12/30/1069027394/omicron-causes-record-breaking-covid-cases-in-the-u-s-and-globally

1094) 2021-12-30 Quintana A: Florida surgeon general unhappy with fed's distribution of monoclonal antibody treatments. WTSP 10 Tampa Bay https://www.wtsp.com/article/news/regional/florida/florida-surgeon-general-monoclonal-antibody-treatment/67-0ad20411-2b32-41ad-bcb2-15d07c5cfc7c

1095) 2021-12-31 FDA: FDA authorizes first two oral antivirals for treatment of COVID-19 | EUA for COVID-19 treatments and tests https://content.govdelivery.com/accounts/USFDA/bulletins/30221ce

1096) 2022-01-03 Anthes E: How accurate are at-home Covid test? Here's a quick guide. The New York Times. https://web.archive.org/web/20220210163820/https://www.nytimes.com/article/at-home-covid-tests-accuracy.html

1097) 2022-01-03 Jewett C: With no way to identify Omicron and Delta patients, treatment decisions are vexing doctors. The New York Times. https://www.nytimes.com/2022/01/03/health/doctors-omicron.html

1098) 2022-01-04 CDC: Understanding mRNA COVID-19 Vaccines. https://www.cdc.gov/TemplatePackage/contrib/widgets/micrositeCollectionViewerMed/index.html?chost=www.muw.edu&cpath=/disease/cdcinfo&csearch=&chash=!%2Fdetail%2F40

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

6795&ctitle=COVID-19%20CDC%20Info%20-%20Disease%20Outbreak%20Information%20-%20MUW&wn=micrositeCollectionViewerMed&wf=/TemplatePackage/contrib/widgets/micrositeCollectionViewerMed/&wid=micrositeCollectionViewerMed1&mMode=widget&mPage=&mChannel=&cdcCollectionid=403305&cdcTheme=theme1&cdcGeotag=%7B%27continent%27:%20%276255149%27,%20%27country%27:%20%276252001%27,%20%27state%27:%20%274436296%27,%20%27region%27:%20%274434357%27%20%7D&cdcDataid=404908&chashOptMode=out#!/detail/413605

1099) 2022-01-04 Cook S, Watson K: U.S. doubling and accelerating order Pfizer antiviral pills. CBS News https://www.cbsnews.com/news/biden-pfizer-covid-pill-antiviral-double-shipment/

1100) 2022-01-06 Biden J: President Biden blasts Trump for 'spreading a web of lies' in a Jan. 6, 2022 speech. https://www.youtube.com/watch?v=bUfyXBmp7S8

1101) 2022-01-07 Yek C, Warner S, Wiltz JL, Sun J, Adjei S, Mancera A, Silk BJ, Gundlapalli AV, Harris AM, Boehmer TK, Kadri SS: Risk factors for severe COVID-19 outcomes among persons aged ≥ 18 years who completed a primary COVID-19 vaccination series – 465 Health Care facilities, United States, December 2020-October 2021. CDC, Morbidity and Mortality Weekly Report (MMWR) https://www.cdc.gov/mmwr/volumes/71/wr/mm7101a4.htm

> Among 1,228,664 persons who completed primary vaccination during December 2020–October 2021, severe COVID-19–associated outcomes (0.015%) or death (0.0033%) were rare. Risk factors for severe outcomes included age ≥65 years, immunosuppressed, and six other underlying conditions. All persons with severe outcomes had at least one risk factor; 78% of persons who died had at least four.

1102) 2022-01-11 American Red Cross: Red Cross declares first-ever blood crisis amid omicron surge. https://www.redcross.org/about-us/news-and-events/press-release/2022/blood-donors-needed-now-as-omicron-intensifies.html

1103) 2022-01-12 Minnesota Department of Health: Ethical framework for allocation of Monoclonal Antibodies during the COVID-19 Pandemic. https://www.health.state.mn.us/diseases/coronavirus/hcp/mabethical.pdf

1104) 2022-01-13 de Vogue A: Supreme Court blocks nationwide vaccine and testing mandate for large businesses, allows health care worker vaccine mandate to take effect. https://www.cnn.com/2022/01/13/politics/supreme-court-vaccine-mandate-covid-19/index.html

1105) 2022-01-18 Mayo Clinic Staff: Different types of COVID-19 vaccines: How they work. https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465 ;

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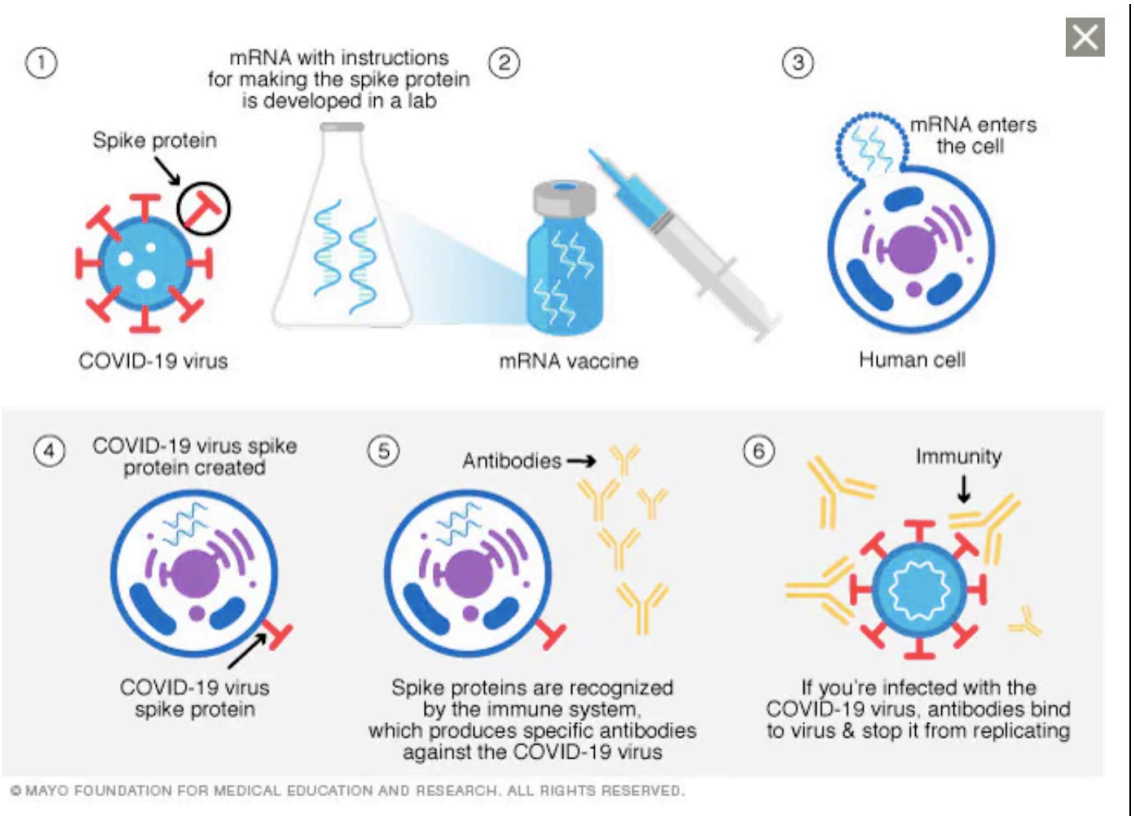
mRNA vaccine cartoon:


1
mRNA with instructions for making the spike protein is developed in a lab
2
3
Spike protein
mRNA enters the cell
COVID-19 virus
mRNA vaccine
Human cell
4
COVID-19 virus spike protein created
5
Antibodies
6
Immunity
COVID-19 virus spike protein
Spike proteins are recognized by the immune system, which produces specific antibodies against the COVID-19 virus
If you're infected with the COVID-19 virus, antibodies bind to virus & stop it from replicating
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mRNA vaccine
A mRNA vaccine is made using mRNA that gives your cells instructions for how to make the spike protein found on the surface of the COVID-19 virus. After vaccination, your immune cells begin making the spike protein and displaying them on cell surfaces. This causes your body to create antibodies that can fight the COVID-19 virus.

https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465#dialogId29607008 ;

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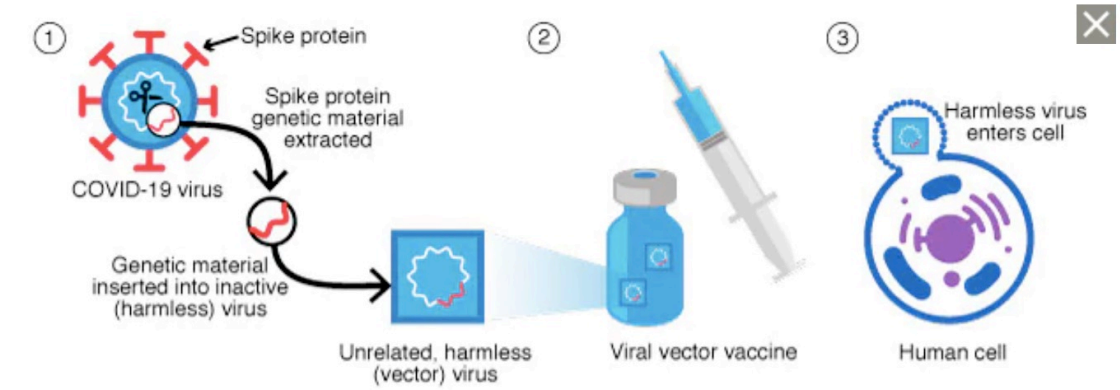
Viral vector vaccine


1
Spike protein
Spike protein genetic material extracted
COVID-19 virus
Genetic material inserted into inactive (harmless) virus
2
Unrelated, harmless (vector) virus
Viral vector vaccine
3
Harmless virus enters cell
Human cell
4
COVID-19 virus spike protein created
COVID-19 virus spike protein
5
Antibodies
Spike proteins are recognized by the immune system, which produces specific antibodies against the COVID-19 virus
6
Immunity
If you're infected with the COVID-19 virus, antibodies bind to virus & stop it from replicating
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Viral vector vaccine

A viral vector vaccine is made when genetic material from a COVID-19 virus is inserted into a unrelated, harmless virus. When the viral vector gets into your cells, it delivers genetic material from the COVID-19 virus that gives your cells instructions for how to make the spike protein found on the surface of the COVID-19 virus. Once your cells displace the spike proteins on their surfaces, your immune system creates antibodies that can fight the COVID-19 virus.

https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465#dialogId17927109 ;

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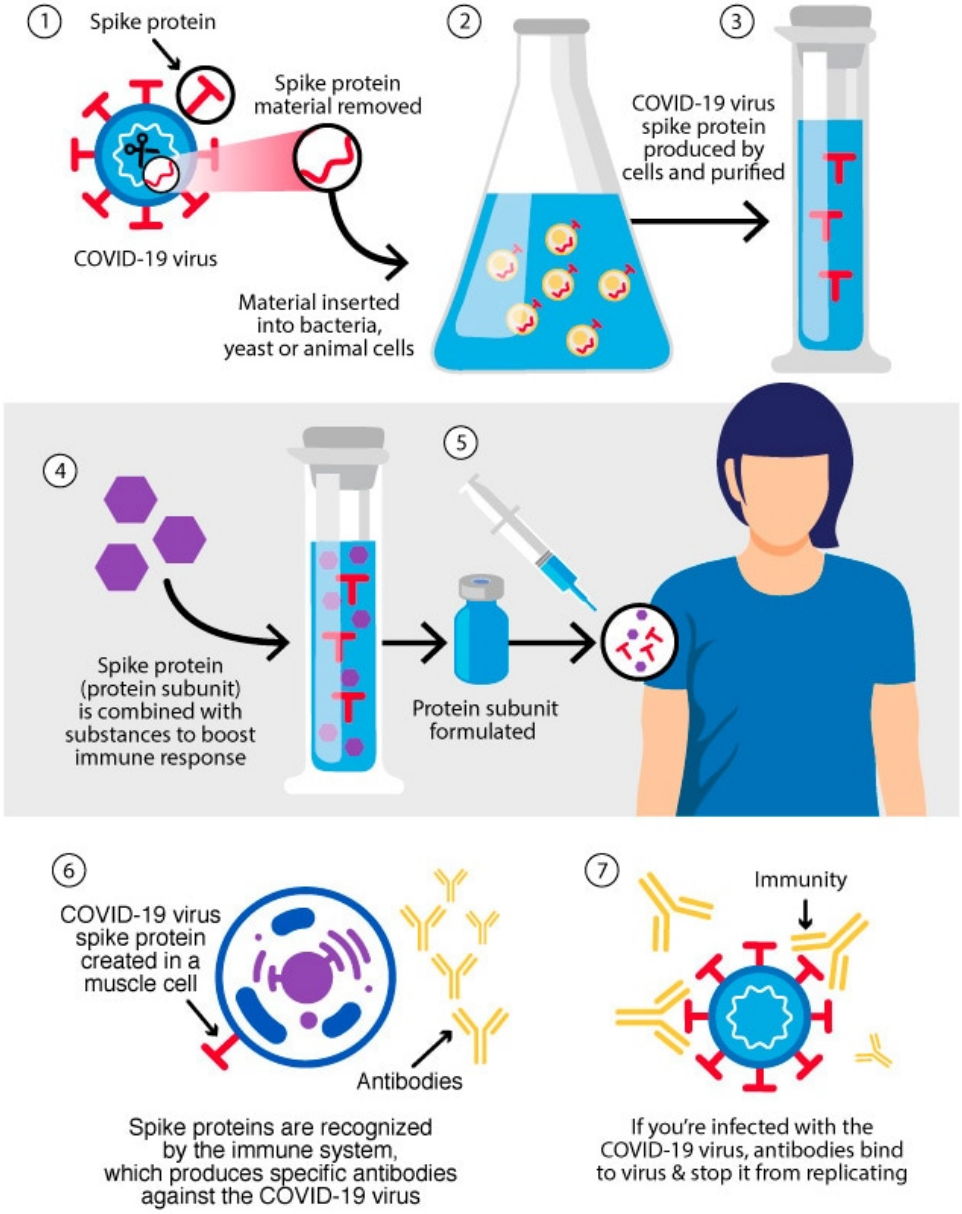
Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

Protein subunit vaccine:


1
Spike protein
Spike protein material removed
COVID-19 virus
Material inserted into bacteria, yeast or animal cells
2
3
COVID-19 virus spike protein produced by cells and purified
4
Spike protein (protein subunit) is combined with substances to boost immune response
5
Protein subunit formulated
6
COVID-19 virus spike protein created in a muscle cell
Antibodies
Spike proteins are recognized by the immune system, which produces specific antibodies against the COVID-19 virus
7
Immunity
If you're infected with the COVID-19 virus, antibodies bind to virus & stop it from replicating

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Protein subunit vaccine

Subunit vaccines include only the parts of a virus that best stimulate your immune system. This type of COVID-19 vaccine contains harmless S proteins. Once your immune system recognizes the S proteins, it creates antibodies and defensive white blood cells. If you later become infected with the COVID-19 virus, the antibodies will fight the virus.

https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465#dialogId5857171

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1106) 2022-01-18 Exact Sciences Corp: Exact sciences presents data showing improved accuracy of second-generation Cologuard test and progress toward and progress toward an even better colorectal cancer screening solution for patients. https://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2022/Exact-Sciences-Presents-Data-Showing-Improved-Accuracy-of-Second-generation-Cologuard-Test-and-Progress-Toward-an-Even-Better-Colorectal-Cancer-Screening-Solution-for-Patients/default.aspx

1107) 2022-01-19 NIH COVID-19 Treatment Guidelines: The COVID-19 Treatment Guidelines Panel's Statement on therapies for high-risk, nonhospitalized patients with mild to moderate COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

1108) 2022-01-21 O'Shaughnessy JA: FDA letter to Gilead Sciences, Inc. …On January 21, 2022, FDA approved a supplemental application to NDA 214787 for Veklury expanding the approved uses to include the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. …now authorizing Veklury for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of are weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are hospitalized, or are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. https://www.fda.gov/media/137564/download

1109) 2022-01-21 FDA: FDA takes actions to expand use of treatment for outpatients with mild-to-moderate COVID-19. https://www.fda.gov/news-events/press-announcements/fda-takes-actions-expand-use-treatment-outpatients-mild-moderate-covid-19

1110) 2022-01-24 Regeneron: U.S. Food and Drug Administration revises Emergency Use Authorization for REGEN-COV® (casirivimab and imdevimab) antibody cocktail due to Omicron Variant. https://investor.regeneron.com/static-files/cf13b06f-b874-4910-b583-c3c93c67a8f8

1111) 2022-01-24 O'Shaughnessy JA: EUA 094 letter to Eli Lilly and Company to limit the use of Eli Lilly's monoclonal antibody cocktail due to resistance of omicron variant. https://www.fda.gov/media/145801/download …On January 24, 2022, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 22, 2021 letter in its entirety, to further limit the use of bamlanivimab and estesevimab administered together for treatment of COVID-19 or as post-exposure prophylaxis of COVID-19 to exclude geographic regions

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where , based on available information including variant susceptibility to these drugs and regional variant frequency, infection, or exposure is likely due to a variant that is non-susceptible to bamlanivimab and etesvimab. Corresponding revisions have also been made to the authorized Fact Sheets.

1112) 2022-01-24 Murphy J: Fauci expects most states to reach peak omicron by February. Close to half already have. NBC News—The Data Point https://www.nbcnews.com/news/all/fauci-omicron-surge-february-2022-states-n1287935

1113) 2022-01-24 U.S. Food & Drug: Coronavirus (COVID-19 update: FDA limits use of certain monoclonal antibodies to treat COVID-19 Due to the Omicron variant. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron

1114) 2022-01-24 Alu A, Chen L, Lei H, Wei Y, Tian X, Wei X: Intranasal COVID-19 vaccines: From bench to bed. The Lancet 2022 Feb 1; 76, 103841. https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(22)00025-1/fulltext

1115) 2022-01-25 Blake A: DeSantis, conservatives erupt over FDA pulling monoclonal antibodies shown to be ineffective against omicron. The Washington Post. https://www.washingtonpost.com/politics/2022/01/25/conservatives-led-by-desantis-erupt-over-another-unproven-coronavirus-treatment/

> …The Food and Drug Administration announced Monday that it would halt emergency-use authorizations for two monoclonal antibody therapies, one made by Regeneron Pharmaceuticals and one by Eli Lilly. At least with these monoclonal antibodies, unlike hydroxychloroquine and ivermectin, there was evidence they were once quite effective; that's just not the situation we find ourselves in at this point.
>
> The FDA decision has led to a vehement outcry from some on the right, including the Republican who has most forcefully promoted monoclonal antibodies: Florida Gov. Ron DeSantis.
>
> DeSantis said Monday that President Biden "has forced medical pros to choose treating their patients or breaking the law."
>
> The governor added Tuesday moring, "Without a shred of clinical data to support its decision, the Biden Administration has revoked the emergency use authorization for lifesaving monoclonal antibody treatments."
>
> DeSantis's criticism has been cheered and echoed by many on the right, including Fox News's Sean Hannity.
>
> Going quite a bit further, DeSantis spokeswoman Christina Pushaw on Monday night even pointed a claim by a conservative conspiracy theorist that "the FDA is trying to make it so that people in Florida die of Covid. They'll kill people to harm Republicans." By Tuesday morning, she promoted another baseless claim that the decision was made "so Fauci-Pfizer can get a few extra points in the stock market."

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> …As Nature reported more than a month ago, preliminary studies suggested that monoclonal antibody therapies, including the ones the FDA has not halted, showed virtually no efficacy against the omicron variant. https://www.nature.com/articles/d41586-021-03829-0
>
> Here are some excerpts from one of the studies, which cites the Regeneron therapy (casirivimab and imdevimab) and the Eli Lilly therapy (bamlanivimab and estesevimab):…

1116) 2022-01-25 U.S. Food and Drug Administration: Emergency Use Authorization. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

1117) 2022-01-25 Troxel AB, Petkova E, Goldfeld K, Liu M, Tarpey T, Wu Y, Wu D, Agarwal A, Avendano-Solá, Brainbridge E, Bar KJ, Devos T, Duarte RF, Gharbharan A, Hsue PY, Kumar G, Luetkemeyer AF, Mayfroidt G, Nicola AM, Mukherjee A, Ortigoza MB, Pirofski LA, Rijders BJA, Rokx C,Sancho-Lopez A, Shaw P, Tebas P, Yoon HA, Grudzen C, J Association of convalescent plasma treatment with clinical status in patients hospitalized with COVID-19, A meta-analysis. JAMA Network | Open. 2022 January 25: 5(1): e2147331: 1-15. https://web.archive.org/web/20220203022011/https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2788377

1118) 2022-01-25 Tin A: How can I get Paxlovid, the COVID-19 pill? Access to COVID treatments remains a challenge. CBS News. https://www.cbsnews.com/news/covid-19-paxlovid-pill-monoclonal-antibodies-treatments/

1119) 2022-01-27 FDA: Know your treatment options for COVID-19. https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-covid-19

1120) 2022-01-27 Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, Oguchi G, Ryan P, Nielsen BU, Brown M, Hidalgo A, Sachdeva Y, Mittal S, Osiyemi O, Skarbinski J, Juneja K, Hyland RH, Osinusi A, Chen S, Camus G, Abdelghany M, davies S, Behenna-renton N, Duff F, Marty FM, Katz MJ, Ginde AA, Brown SM, Schiffer JT, a d Hill JA for the GS-US-540-9012 (PINETREE) Investigators. Early Remdesivir to prevent progression to severe Covid-19 in outpatients. New Engl J Med 2022 Jan 27; 386 (4): 305-315. https://www.nejm.org/doi/full/10.1056/NEJMoa2116846 with Supplementary Appendix https://www.nejm.org/doi/suppl/10.1056/NEJMoa2116846/suppl_file/nejmoa2116846_appendix.pdf

1121) 2022-02 Paneth N, Casadevall A, Pirofski L, Henderson JP, Grossman BJ, Shoham S, Joyner MJ: WHO covid-19 drugs guideline: reconsider using convalescent plasma. BMJ 2022 February; 376: o295. https://www.bmj.com/content/376/bmj.o295

1122) 2022-02 Alu A, Chen L, Yuquan HL, Tian WX, Wei X: Intranasal COVID-19 vaccines: From bench to bed. www.thelancet.com 2022 Feb; 76: 1-16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8785603/pdf/main.pdf

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1123) 2022-02-01 NIH: COVID-19 Treatment Guidelines: Anti-SARS-CoV-2 Monoclonal Antibodies. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

1124) 2022-02-03 IDSA Guideline on the Treatment and Management of COVID-19: Convalescent Plasma. https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt---convalescent-plasma-2022-02-03.pdf

1125) 2022-02-06 Gastroenterology consultants of San Antonio: The truth about Cologuard tests. https://www.gastroconsa.com/the-truth-about-cologuard-tests/

1126) 2022-02-11 O'Shaughnessy JA: FDA EUA letter to Eli Lilly and Company: Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Betelovimab is not FDA approved for any uses, including use as treatment for COVID-19. https://www.fda.gov/media/156151/download

1127) 2022-02-11 FDA News Release: Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against omicron variant. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains#:~:text=The%20FDA%20is%20carefully%20monitoring,2%20omicron%20subvariant.

1128) 2022-02-14 Forman R: COVID Booster goes to the nasal cavity, where it will be most effective—Iwasaki A. Yale School of Medicine. https://medicine.yale.edu/news-article/nasal-approach-to-covid-vaccination-gains-traction-at-yale/

1129) 2022-02-15 Herscher M: Nearly half of state mask mandates have ended in the past 3 weeks. NBC News –The Data Point. https://www.nbcnews.com/news/us-news/mask-mandate-map-february-2022-n1289093

1130) Ducharme J: Nasal vaccines could help stop COVID-19 from spreading – If scientists can get them right. TIME. https://time.com/6148257/nasal-vaccines-covid-19/

1131) 2022-02-16. Andrus CH: Thank you letter to Gilead Sciences for providing the reference regarding the date of completion of Phase 1 remdesivir trial.

> **From:** Charles.Andrus@va.gov,
> **To:** Public_affairs@gilead.com,
> **Cc:** Charles.Andrus@va.gov, candrus600@aol.com, Anthony.Fauci@nih.hhs.gov, kara.harris@nih.hhs.gov, Janet.Woodcock@fda.hhs.gov, Denise.Hinton@hhs.gov, Jacqueline.OShaughnessy@fda.hhs.gov, michael.hogan@va.gov,
> **Subject:** RE: Phase 1 remdesivir trial result
> **Date:** Wed, Feb 16, 2022 3:25 pm
> **Attachments:** 3 Andrus SLU cv 8_11_2021.docx (7964K),

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

2/16/2022

NIAID Case #12276

Dear Gilead:

Thank you for forwarding this article to me: Humeniuk R, Mathias A, Huyen C, Osinusi A, Shen G, Chng E, Ling J, Wu A, German P: Safety, Tolerability, and Tolerability, and Pharmacokinetic of Remdesivir, An antiviral for Treatment of COVID-19, in Healthy Subjects. Clin Transl Sci 2020; 13, 896-906: Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID 19, in Healthy Subjects (wiley.com). I have attached a copy of my CV so you know who I am. Over my decades of involvement with the Veterans Health Administration (VHA), U.S. Department of Veterans, I have attempted to be an advocate for each and every individual Veteran patient that presented to me. My biggest challenge was to have the phrase in VHA Handbook 1400.1 on Resident Supervision revised (after ~50 years): **Level 3: Attending Surgeon not present, immediately available.** What was condoned by the inappropriate application of Level 3 was that on nights, weekends, holidays, family get togethers, etc., some University Attending Surgeons would staff residents in the OR from afar (ghost surgery). Twenty years ago, I fought for that change all the way to the U.S. Court of Appeals for the Federal Circuit in *Andrus v VA*, Case 03-3162—in which the court *per curium* "failed to rule." I lost all my battles with the VA; but, in the end, all Attending Surgeons-of-Record in the VA today are required to be present in the OR suite during every individual Veterans' operation which is definitely to the betterment of every Veteran patient. The VA saved face by: 1.) changing VAH Handbook from 1400.1 to VAH Handbook 1400.01 so you can't find previous versions electronically if you don't know the previous URL.; 2.) as is common practice today, in the agencies of the Executive Branch of the Federal Government, electronically overwrite documents without designating what has been rescinded or that there was even a previous document; and 3.) I became and still am an *unperson* in the VA from 4/1982-8/2016 since my Official Personnel File (OPF) has been misplaced/lost. Thus, from April 1982 to August 2016, I don't exist in the VA until I returned in August 2016, as an Attending Physician and General Surgeon at the St. Louis VAMC. My VA service from 1982 to 2002 does not exist "officially" even though from 8/1996 to 1/2002, I was the Chief of Surgery, Edward Hines, Jr. VAH (the first hospital of the University-VA affiliation in 1946 under PL-79-293); and I was interviewed for the position of Under Secretary for Health

(USH) of the Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (DVA) on the 10th floor of VACO (across Lafyette Square from *The White House*) on the afternoon of December 10, 1999. I am telling you this, so I can put in context for you the convoluted process regarding Remdesivir that parallels that which occurred to me in my fight to stop Physically Unsupervised resident surgeons by VA misdirection and obfuscation twenty years ago. Today, by changing URLs, electronic overwriting, and semantics, the FDA, the NIH, the CDC, the VA, etc. have somewhat stretched the truth before the American people.

I thank you for forwarding the reference regarding the Phase I studies completed for Remdesivir (RDV). As is quoted in the article:

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On May 1, 2020, based on available data from to global clinical trials, the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-

19[19,22,23] Based on these clinical data, RDV has been approved for the treatment of adults and pediatric patients in

Japan.[24] This paper describes the safety and pharmacokinetics (PKs) of the solution and lyophilized formulations of i.v. RDV administered to healthy participants in the two first-in-human (FIH) phase I studies.

The above paragraph suggests that the FDA issued the EUA after review of the two first-in-human phase I studies involving Remdesivir (VEKLURY) and that review occurred at least by May 1, 2020, which means that phase I human trials were deemed safe and implies that the phase I trials *de facto* were completed—BUT, that presented multiple ethical and legal dilemmas for the FDA, the NIH, etc.

1. The FDA issued the first Remdesivir EUA on May 1, 2020 (which was the date when Dr. Fauci announced Remdesivir from the Oval Office); yet by making it an EUA, Remdesivir,-- the FDA was defining Remdesivir as an "unapproved" drug in the treatment of COVID-19

2. As phase II/III clinical trials proceeded, prospective participants who had contracted COVID-19 should have been made aware in their Informed Consent that with The Right to Try Act, PL-115-176 that they could still be afforded Remdesivir by non-participation in the mandated RCT placebo trials—for that matter, all of America should have been told of this by the FDA! As the Phase I studies *de facto* were completed, any American could have asked for Remdesivir under PL-115-176 and should have received it!

3. As I am sure that you are well-aware that Remdesivir is "a single diastereomeric monophoramidate prodrug that inhibits viral RNA polymerases" which works best during the initial viremic phase of COVID-19—rather than in the later severe disease phases of cytokine cascade and bradykinin storm. Unfortunately, with the issuance of the EUA on May 1, 2020, "the US Food and Drug Administration **(FDA) granted emergency use authorization** to allow RDV to treat adults and children **hospitalized with severe COVID-19**[19,22,23]." In fact, the **FDA removed the severity stipulation quietly**--not notifying the American public of this significant retraction--on **August 28, 2020**. In the FDA January 21, 2022 letter to Madelyn Low, MBS, Manager, Regulatory Affairs, Gilead Sciences, Inc., https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fda-authorization-letter.pdf?la=en&hash=FD3737583BE0E4DF710ADB36AEAA2DBD, there are 8 references on pages 1 and 2 in which the Acting Chief Scientist of FDA outlined the chronology regarding Remdesivir including the August 28, 2020 retraction of the severity of illness stipulation: "...FDA revised authorized use of Veklury to no longer limit its use for the treatment of patients with severe disease." (How could Remdesivir being an "unapproved" drug in the treatment of COVID-19 under the FDA's EUAs standards become a drug that the FDA was officially revising authorization so it could be given early in the course of the disease? It seems like a bunch of semantics; but if that bunch of semantics limits the rights of individuals in America, that is wrong.

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4. “On October 22, 2020, FDA also approved NDA 214787 for Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 Kg) **requiring hospitalization.”** At this point, Remdesivir (VEKLURY) was designated by the FDA as a prescription drug (NDA 214787) on October 22, 2020.

5. In November 2020, the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs issued for the fully-FDA- authorized-prescription drug, VEKLURY, NDA 214787 the: “Remdesivir (VEKLURY) Criteria for Use” of how to administer Remdesivir with the severity Inclusion Criteria exclusively included that had been removed previously on August 28, 2020 by the FDA:

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY)
Criteria for Use
November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive remdesivir

- ☐ Treated for COVID-19 as an outpatient
- ☐ AST or ALT > 5 times the upper limit of normal
- ☐ Hospitalized patients but NOT requiring supplemental oxygen*
- ☐ Concomitant use of hydroxychloroquine or chloroquine
- ☐ Current eGFR < 30 mL/min**

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

- ☐ Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

Supplemental Information

Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given

**Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis*

***Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.*

****Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19*

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

1

Updated version may be found at PBM.INTERnet or PBM.INTRAnet

6. When I had a patient denied Remdesivir by the Infectious Diseases service quoting the November VA directive, I contacted Richard Stone, M.D., VHA Chief Medical Executive (the Trump Administration’s title for the Under Secretary for Health, VHA, DVA). Dr. Stone contacted VA Pharmacy Management Services and the Medical Advisory Board. At first, the VA responded

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to me. But when the VA became evasive, I contacted the FDA, the NIAID (Case #12276), and wrote a letter to the editors of the *The New England Journal of Medicine*. None responded to me.

7. I recently had a patient admitted to the Surgical Service who had newly turned COVID-19 positive (less than 24 hours from negative to positive). The recommendations from the same Infectious Diseases service was that if the patient had any symptomatology like headache or neck pain, give three days of Remdesivir; and if the patient develops a cough, give five days of Remdesivir and dexamethasone. By the time of that consult, the CDC had stated a month before that Regeneron's and Eli Lilly's monoclonal cocktails were ineffective against COVID-19, omicron variant; and, thus, GlaxoSmithKline's *sotrovimab* was and is being *de facto* rationed at present time.

Once again, I thank all involved in addressing my question at Gilead regarding if a phase I study had been completed in the case of Remdesivir. You were all very professional and willing to listen—and, most of all, my personal thanks as a Federal Physician and Surgeon for you have provided this information which may become an outstanding service for the people of the United States of America.

Thank you,
Charles Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine

Chief and Attending General Surgeon, Unit II (SLU) General Surgery division, Surgical Service, John Cochran (112JC), St. Louis, MO 63106

Office phone: 314-652-4100 ext 54463 Beeper: 314-491-2417
Home phone: 314-455-9482

P.S. I hope this e-mail will initiate an overall discussion regarding transparency by the agencies of the U.S. Government in regards to the EARLY (< 72 hours from diagnosis) administration with intent of synergism of COVID-19 Convalescent Plasma, COVID-19 monoclonal antibodies, Remdesivir and other future antivirals, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.

From: Public Affairs <Public_affairs@gilead.com>
Sent: Wednesday, February 16, 2022 7:54 AM
To: Andrus, Charles H. (STL) <Charles.Andrus@va.gov>
Subject: [EXTERNAL] Phase 1 remdesivir trial results

Dr. Andrus,

You can find the published results of the Phase 1 remdesivir trial here:
https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.12840 *(reference #466 of this chronological bibliography)*

Thank you for your inquiry,

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Gilead Public Affairs

1132) 2022-02-22 Adler B: Trump praises Putin's 'genius' incursion into Ukraine. https://news.yahoo.com/trump-praises-putins-genius-incursion-into-ukraine-234001858.html

1133) 2022-02-25 CDC: COVID-19—People with certain medical conditions. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

1134) 2022-02-27 Campbell C: 'Almost treasonous': Romney condemns GOP backing Putin. https://www.aol.com/news/almost-treasonous-romney-condemns-gop-171557057.html

1135) 2020-02-27 Moore M: US hints at war-crimes tribunal after Ukraine accuses Russia of genocide. New York Post. https://nypost.com/2022/02/27/us-hints-at-war-crimes-tribunal-after-ukraine-accuses-russia-of-genocide/

1136) 2022-02-27 Reuters: World Court: Ukraine has filed suit against Russia, citing false genocide claims. https://www.reuters.com/world/europe/icc-says-may-investigate-possible-war-crimes-after-russian-invasion-ukraine-2022-02-25/

1137) 2022-02-27 Bancroft H, Gregory A, Rai A: Ukraine-Russian news live: Putin puts nuclear forces on high alert as Zelensky calls for foreign fighters. Independent. https://www.independent.co.uk/news/world/europe/russia-ukraine-crisis-latest-putin-kyiv-zelensky-war-update-b2024247.html

1138) 2022-02-28 iSpot.tv: Pfizer, Inc. TV Spot, 'Move Fast: Oral Treatment. https://www.ispot.tv/ad/bAea/pfizer-inc-move-fast-oral-treatment

DEAR MR. PRESIDENT:

WHAT FOLLOWS IS THE FDA DISCLAIMER REGARDING THE ADVERTIZEMENT IN WHICH THE "ORAL MEDICATION in the treatment of COVID-19" IS AUTHORIZED UNDER AN EUA BUT NOT APPROVED BY THE FDA FOR THE USE TO TREAT EARLY (<120 HOURS FROM ONSET) COVID 19.

Mr. President: You may ask, Why the legal semantics? Well, it is probably a violation of Federal Law that Pfizer is advertising Paxlovid (the advertisement never calls the antiviral by name—as Merck also has an experimental oral antiviral authorized by the FDA under an EUA and both are under EUAs); ***while*** Remdesivir (VEKLURY) **HAS BEEN AN FDA approved and authorized PRESCRIPTION intravenous antiviral DRUG**

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

designated FOR use in THE EARLY TREATMENT OF COVID-19 SINCE October 22, 2020. In short, your administration has bought 20 million boxes (30 pills per box (1 five day treatment dose) for a total of 600 million—0.6 billion pills—of an experimental antiviral, PAXLOVID, in the "TEST to TREAT initiative"—which is outstanding. These experimental oral antivirals under EUAs are in direct commercial competition with an FDA approved, authorized intravenous prescription drug: VEKLURY (Remdesivir) which could have been administered in EVERY INFUSION CENTER, OUTPATIENT SURGICENTER, AND HOSPITAL IN THE U.S.A. FOR THE LAST 20 MONTHS—but was withheld by general medical ignorance, the pharmaceutical industry's arrogance and greed, and federal incompetence and conflicts-of-interests.

Charles H. Andrus, M.D., F.A.C.S., May 15, 2022

https://www.covid19oralrx-patient.com/?source=google&HBX_PK=s_paxlovid&skwid=43700068270576697&gclid=EAIaIQobChMIsIiA49fY9gIVk5JbCh0sxA4PEAAYASAAEgLZs_D_BwE&gclsrc=aw.ds

Authorized Use

The FDA has authorized the emergency use of PAXLOVID, an investigational medicine, for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with a positive test for the virus that causes COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under an EUA.

PAXLOVID is investigational because it is still being studied. There is limited information about the safety and effectiveness of using PAXLOVID to treat people with mild-to-moderate COVID-19.

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
Prevention: *Active Immunization*: Vaccines

Pfizer

PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets)

Now Authorized for Emergency Use

PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

1139) 2022-03-01 Biden J: Remarks of President Joe Biden – State of the Union Address as Prepared for Delivery. *The White House, Briefing Room, March 1, 2022, Speeches and Remarks.* https://www.whitehouse.gov/briefing-room/speeches-remarks/2022/03/01/remarks-of-president-joe-biden-state-of-the-union-address-as-delivered/

> …I remember when my Dad had to leave our home in Scranton, Pennsylvania to find work. I grew up in a family where if the price of food went up, you felt it.
>
> That's why one of the first things I did as President was fight to pass the American Rescue Plan.
>
> Because people were hurting. We needed to act, and we did.
>
> Few pieces of legislation have done more in a critical moment in our history to lift us out of crisis.
>
> It fueled our efforts to vaccinate the nation and combat COVID-19. It delivered immediate economic relief for tens of millions of Americans.
>
> Helped put food on their table, keep a roof over their heads, and cut the cost of health insurance.
>
> And as my Dad used to say, it gave people a little breathing room.
>
> And unlike the $2 Trillion tax cut passed in the previous administration that benefitted the top 1% of Americans, the American Rescue Plan helped working people—and left no one behind. …
>
> … For more than two years, COVID-19 has impacted every decision in our lives and the life of the nation.
>
> And I know you're tired, frustrated, and exhausted.
>
> But I also know this.
>
> Because of the progress we've made, because of your resilience and the tools we have, tonight I can say

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we are moving forward safely, back to more normal routines.

We've reached a new moment in the fight against COVID-19, with severe cases down to a level not seen since last July.

Just a few days ago, the Centers for Disease Control and Prevention—the CDC—issued new mask guidelines.

Under these new guidelines, most Americans in most of the country can now be mask free.

And based on the projections, more of the country will reach that point across the next couple of weeks.

Thanks to the progress we have made this past year, COVID-19 need no longer control our lives.

I know some are talking about "living with COVID-19". Tonight – I say that we will never just accept living with COVID-19.

We will continue to combat the virus as we do other diseases. And because this is a virus that mutates and spreads, we will stay on guard.

Here are four common sense steps as we move forward safely.

First, stay protected with vaccines and treatments. We know how incredibly effective vaccines are. If you're vaccinated and boosted you have the highest degree of protection.

We will never give up on vaccinating more Americans. Now, I know parents with kids under 5 are eager to see a vaccine authorized for their children.

The scientists are working hard to get that done and we'll be ready with plenty of vaccines when they do.

We're also ready with anti-viral treatments. If you get COVID-19, the Pfizer pill reduces your chances of ending up in the hospital by 90%.

We've ordered more of these pills than anyone in the world. And Pfizer is working overtime to get us 1 Million pills this month and more than double that next month.

And we're launching the "Test to Treat" initiative so people can get tested at a pharmacy, and if they're positive, receive antiviral pills on the spot at no cost.

If you're immunocompromised or have some other vulnerability, we have treatments and free high-quality masks.

We're leaving no one behind or ignoring anyone's needs as we move forward.

And on testing, we have made hundreds of millions of tests available for you to order for free.

Even if you already ordered free tests tonight, I am announcing that you can order more from covidtests.gov starting next week.

Second – we must prepare for new variants. Over the past year, we've gotten much better at detecting new variants.

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If necessary, we'll be able to deploy new vaccines within 100 days instead of many more months or years.

And, if Congress provides the funds we need, we'll have new stockpiles of tests, masks, and pills ready if needed.

I cannot promise a new variant won't come. But I can promise you we'll do everything within our power to be ready if it does.

Third – we can end the shutdown of schools and businesses. We have the tools we need.

It's time for Americans to get back to work and fill our great downtowns again. People working from home can feel safe to begin to return to the office.

We're doing that here in the federal government. The vast majority of federal workers will once again work in person.

Our schools are open. Let's keep it that way. Our kids need to be in school.

And with 75% of adult Americans fully vaccinated and hospitalizations down by 77%, most Americans can remove their masks, return to work, stay in the classroom, and move forward safely.

We achieved this because we provided free vaccines, treatments, tests, and masks.

Of course, continuing this costs money.

I will soon send Congress a request.

The vast majority of Americans have used these tools and may want to again, so I expect Congress to pass it quickly.

Fourth, we will continue vaccinating the world.

We've sent 475 Million vaccine doses to 112 countries, more than any other nation.

And we won't stop.

We have lost so much to COVID-19. Time with one another. And worst of all, so much loss of life.

Let's use this moment to reset. Let's stop looking at COVID-19 as a partisan dividing line and see it for what it is: A God-awful disease.

Let's stop seeing each other as enemies, and start seeing each other for who we really are: Fellow Americans.

We can't change how divided we've been. But we can change how we move forward—on COVID-19 and other issues we must face together. …

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> …And fourth, let's end cancer as we know it.
>
> This is personal to me and Jill, to Kamala, and to so many of you.
>
> Cancer is the #2 cause of death in America–second only to heart disease.
>
> Last month, I announced our plan to supercharge
> the Cancer Moonshot that President Obama asked me to lead six years ago.
>
> Our goal is to cut the cancer death rate by at least 50% over the next 25 years, turn more cancers from death sentences into treatable diseases.
>
> More support for patients and families.
>
> To get there, I call on Congress to fund ARPA-H, the Advanced Research Projects Agency for Health.
>
> It's based on DARPA—the Defense Department project that led to the Internet, GPS, and so much more.
>
> ARPA-H will have a singular purpose—to drive breakthroughs in
> cancer, Alzheimer's, diabetes, and more.

1140) 2022-03-01 Satyanarayana M: Nasal spray COVID preventives are finally in development – Different methods of drug delivery give us more tools to fight disease. Scientific American. https://www.scientificamerican.com/article/nasal-spray-covid-preventives-are-finally-in-development1/

1141) 2022-03-06 Brewster A, Gomez Fin: Trump renews NATO criticism after Russia's invasion of Ukraine, and also say "vote counter" can be more important than candidate. CBS News https://www.cbsnews.com/news/trump-russia-ukraine-nato-elections/

> Trump's remarks came about 24 hours after former Vice President Mike Pence took several shots at Trump during his address to the same donor retreat, which is taking place in New Orleans.
>
> Pence told them Friday evening that "there is no room in this party for apologists for Putin" — days after Trump had referred to the Russian president as "smart" and "savvy." On Saturday evening, Trump mentioned that "somebody called me a Putin apologist the other day," but didn't bring up Pence, according to a source.

1142) 2022-03-07 Casadevall A, Grossman BJ, Joyner MJ, Henderson JP, Paneth N, Pirofski LA, Shoham S: National COVID-19 Convalescent Plasma Project. Last digitized for International Archive, March 7, 2022. https://ccpp19.org/about/index.html

1143) 2022-03-08 HHS.gov: Fact Sheet: Biden administration launches nationwide Test-to-Treat initiative ensuring rapid 'On the Spot' access to lifesaving COVID treatments. https://www.hhs.gov/about/news/2022/03/08/fact-sheet-biden-administration-launches-

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nationwide-test-treat-initiative-ensuring-rapid-on-spot-access-lifesaving-covid-treatments.html

1144) 2022-03-09 Rubin R: Once viewed as a promising COVID-19 treatment, convalescent plasma falls out of favor. JAMA network https://jamanetwork.com/journals/jama/fullarticle/2790074?guestAccess

In the pandemic's initial dark days, physicians and patients and their families were desperate for effective COVID-19 treatments. They didn't yet have monoclonal antibodies or antiviral pills to lessen the ravages of the disease, so many turned to a therapy more than a century old.

At the very least, they figured, convalescent plasma, donated by people who'd recovered from COVID-19, couldn't hurt, and the SARS-CoV-2 antibodies it was presumed to contain could enhance patients' defenses against COVID-19.

"There was a preconceived notion of efficacy," H. Clifford Lane, MD, deputy director for clinical research and special projects at the National Institute of Allergy and Infectious Diseases, said in a recent interview.

Three reports from Wuhan, China, published in 2020 in *JAMA*, the *Proceedings of the National Academy of Sciences*, and the *Journal of Medical Virology*, showed that patients' viral load decreased and their symptoms improved following infusions of convalescent plasma. But the studies involved only a total of 21 patients; the authors of all 3 articles noted that clinical trials were needed to confirm the findings.

Nevertheless, while trials were being planned, US hospitals began infusing patients with COVID-19 with convalescent plasma through the US Food and Drug Administration's (FDA's) Expanded Access Program (EAP). Approximately 94 000 people hospitalized with COVID-19 in the US had received convalescent plasma infusions by August 2020, when the FDA ended the EAP and authorized the golden liquid for emergency use.

A December 2021 analysis of EAP data in *PLOS Medicine* demonstrated convalescent plasma's safety in patients hospitalized with COVID-19—the incidence of serious adverse events was less than 1%. But because the study didn't include a control or comparator group, "the data should not be used to infer definitive treatment effects," the authors noted.

As other COVID-19 treatments became available, convalescent plasma's early promise didn't pan out in randomized clinical trials. "I don't think convalescent plasma is a first-line therapy at this point," Kevin Schulman, MD, a professor of medicine at the Stanford University School of Medicine who has studied the treatment, said in an interview.

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Panic Instead of Science?

Convalescent plasma wasn't associated with clinical benefit in a recent *JAMA Network Open* meta-analysis that pooled findings from 8 randomized clinical trials involving 2341 hospitalized patients breathing without the aid of mechanical ventilation, 1231 of whom received the treatment.

A UK trial published too recently to be considered for inclusion in the meta-analysis reached a similar conclusion. It randomized 11 558 hospitalized patients—5% of whom were receiving invasive mechanical ventilation upon randomization—to receive usual care plus convalescent plasma or only usual care. Researchers found that convalescent plasma did not improve survival or progression to ventilation.

In addition, a recently published multicenter placebo-controlled trial randomized 511 high-risk outpatients with COVID-19 who came to emergency departments within 7 days of symptom onset. The study found that convalescent plasma didn't prevent disease progression.

"We've moved on," said Schulman, a coauthor of the emergency department trial. "Convalescent plasma is a great thing to think about very early in a pandemic."

Instead of providing an untested treatment to tens of thousands of patients in the EAP, multiple, large clinical trials could have been conducted, Schulman said. But, he added, a "huge amount of desperation" early in the pandemic "turned into panic, not into science."

Large clinical trials, with 2500 patients apiece, could have answered questions that still remain, such as identifying the optimal dose and timing of convalescent plasma treatment and which patients are likely to benefit, Schulman said.

"You could easily argue we underdosed patients" in his trial, Schulman acknowledged. "Our trial was the best we could do at the time."

All in the Timing?

Arturo Casadevall, MD, PhD, a leader of the National COVID-19 Convalescent Plasma Project, isn't ready to abandon a treatment he's championed since penning a *Wall Street Journal* op-ed about it in February 2020.

"In the spring of 2020, I really thought that convalescent plasma was a safety raft to new therapies that would be available in the fall," Casadevall, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, said in a recent interview.

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Casadevall said he would have liked to conduct clinical trials with some of the patients enrolled in the EAP, but funding wasn't available. Instead, he took a different approach to try to assess convalescent plasma's efficacy: He tracked the number of convalescent plasma units that blood banking organizations dispensed to hospitals per admission and COVID-19 deaths in the fall of 2020. Casadevall and his collaborators found a strong inverse correlation between convalescent plasma use per COVID-19 hospital admission and deaths from the disease occurring 2 weeks after admission.

The problem with the randomized trials is that they didn't treat patients soon enough to make a difference, Casadevall said.

Only trials in which patients receive convalescent plasma early in their infection could be expected to show a treatment benefit, he explained. By the time patients require hospitalization for COVID-19, the horse is already out of the barn. At that point, Casadevall said, inflammation is the problem, so anti–SARS-CoV-2 antibodies wouldn't help slow disease progression. (Similarly, no anti–SARS-CoV-2 monoclonal antibody product has been authorized for patients with severe COVID-19.) The National COVID-19 Convalescent Plasma Project has posted critiques of Schulman's study, the UK trial, and other research on its website.

Casadevall coauthored a recent multicenter trial that randomized 1225 outpatients whose COVID-19 symptoms had begun within 8 days before enrollment. The study, which hasn't been peer-reviewed, found that early administration of high-titer SARS-CoV-2 convalescent plasma reduced hospitalizations over the next 28 days by 54% compared with control plasma from donors who had not had COVID-19.

"High titer convalescent plasma is an effective early outpatient COVID-19 treatment with advantages of low cost, wide availability, and rapid resilience to variant emergence from viral genetic drift in the face of a changing pandemic," Casadevall and his coauthors concluded.

Limiting Its Use

Despite Casadevall's favorable finding, recently updated guidelines from the World Health Organization (WHO), the FDA, and the Infectious Diseases Society of America (IDSA) recommend only limited use of convalescent plasma, if that.

On February 8, 2022, IDSA strongly recommended against using convalescent plasma in patients hospitalized with COVID-19. Among ambulatory patients with mild to moderate disease who are at high risk of progression to more serious symptoms and have no other treatment options, infusing high-titer COVID-19 convalescent plasma within 8 days of symptom onset is better than not infusing it, according to the guideline, which described this as a conditional recommendation with low certainty of evidence.

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The FDA's most recent revision of the Emergency Use Authorization (EUA) for COVID-19 convalescent plasma, published December 28, 2021, limits treatment with high-titer COVID-19 convalescent plasma to patients who have immunosuppressive disease or are receiving immunosuppressive treatment.

Randomized clinical trials and observational studies show that convalescent plasma is unlikely to be associated with clinical benefit in immunocompetent individuals with COVID-19, according to the FDA.

Interestingly, the WHO recommends against its use for patients who *aren't* severely ill, calling the evidence for that position "certain." Convalescent plasma should be used only within clinical trials for severe and critical patients with COVID-19, the WHO said in December 2021.

In a letter to the *BMJ*, Casadevall and coauthors urged the WHO to reconsider, saying that the organization "avoided digging below the surface to ask critical questions about treatment timing, study populations, and antibody titre" of the convalescent plasma in the trials it considered.

For now, demand for convalescent plasma is low because the clinical trial findings in hospitalized patients have persuaded many physicians that it won't benefit any patients, Casadevall said. On top of that, he said, "Medicine has gotten used to working with therapies that are very well-defined. Plasma is a therapy where physicians are uncomfortable because every unit is different. To many people, that just doesn't feel right."

Lane is among those people. "It's not a uniform product," he noted. Assays suggested by the FDA measure only antibodies to the spike protein of 1 variant, so it's difficult to know the true level and nature of antibodies in a unit of convalescent plasma, Lane said.

And it's virtually impossible to judge a unit of plasma by its donor, Lane said. "Typically, the sicker you are, the better your antibodies." Younger people also tend to generate more antibodies than older people, he added. However, "the immune response to SARS-CoV-2 is highly variable."

Other COVID-19 treatments are standardized, so physicians can know exactly what they're giving patients, Lane said. "If you have an at-risk ambulatory patient with symptoms, you can give them Paxlovid [nirmatrelvir and ritonavir, Pfizer's antiviral pill], you can give them remdesivir. You can reduce their risk of being hospitalized 80% to 85%, and you know what you've given."

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Published Online: March 9, 2022. doi:10.1001/jama.2022.3214

Conflict of Interest Disclosures: Dr Schulman reports receiving personal fees from Novartis and from Frazier Healthcare Partners. Dr Casadevall reports that he is involved in convalescent plasma clinical trials at Johns Hopkins and serves on the scientific board of SAB Biotherapeutics, an antibody company.

1145) 2022-03-10 Takashita E, Kinoshita N, Kawaoka Y, and Others: Efficacy of antibodies and antiviral drugs against Covid-19 omicron variants. N Eng J Med 2022 March 10; 386(10): 995-998. https://www.nejm.org/doi/pdf/10.1056/NEJMc2119407?articleTools=true

1146) 2022-03-10 Katella K: 12 things to know about Paxloid, the latest COVID-19 pill. Yale Medicine https://www.yalemedicine.org/news/12-things-to-know-paxlovid-covid-19

1147) 2022-03-11 Adams B: Pfizer's softly, softly, COVID marketing approach continues with new drug ad FIERCE Pharma. https://www.fiercepharma.com/marketing/pfizers-softly-softly-marketing-approach-continues-new-paxlovid-covid-drug-ad

1148) 2022-03-11 Ellis R: Scientists identify new COVID variant called 'Deltacron'. WebMD https://www.webmd.com/lung/news/20220311/new-covid-variant-deltacron#:~:text=March%2011%2C%202022%20%2D%2D%20A,the%20World%20Health%20Organization%20says.

1149) 2022-03-14 Federal Trade Commission (FTC): Truth in Advertising. https://www.ftc.gov/news-events/topics/truth-advertising

1150) 2022-03-16 National COVID-19 Convalescent Plasma Project: National COVID-19 Convalescent Plasma Project. News – Critiques of Trials. Last digitized capture by the Internet Archive, March 16, 2022. https://ccpp19.org/news/index.html

1151) 2022-03-17 FDA: EUA 105 letter to Pfizer regarding PAXLOID [nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentration to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOID is not approved for any use, including treatment of COVID-19.] https://www.fda.gov/media/155049/download

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

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Treatment: *Passive Immunization*: COVID-19 Convalescent Plasma and Antibodies and *Antivirals*
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• Distribution of the authorized PAXLOVID will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s)[4], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

• PAXLOVID may only be used by healthcare providers to treat mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk[5] for progression to severe COVID-19, including hospitalization or death;

Limitations on Authorized Use

• PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.[6]
• PAXLOVID is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
• PAXLOVID is not authorized for use for longer than 5 consecutive days.

• PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).[7]

• The use of PAXLOVID covered by this authorization must be in accordance with the authorized Fact Sheets.

1152) 2022-03-17 Shasteen H: Intranasal COVID vaccine offers hope against subvariants. Biospace https://www.biospace.com/article/intranasal-covid-vaccine-offers-hope-against-subvariants/

1153) 2022-03-18 BJC HealthCare, Washington University Physicians: COVID-19 Adult Treatment Guidance. https://www.bjc.org/for-physicians/covid Algorithm for Decision: https://www.bjc.org/Portals/0/Coronavirus/BJC_WashU_Outpatient_Therapeutics_Decision_Algorithm_3.2.22.pdf

1154) 2022-03-20 McConnell M, Brennan M: ICYMI: McConnell on 'Face the Nation', CBS News. https://www.republicanleader.senate.gov/newsroom/videos/watch/icymi-mcconnell-on-face-the-nation Transcripts: https://www.cbsnews.com/news/mitch-mcconnell-transcript-face-the-nation-03-20-2022/

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On Friday evening, 3/28/2025, it was announced that Peter Marks, M.D., PhD resigned from the FDA as the "top vaccine scientist." This statement of "top vaccine scientist" was *palteringly* incorrect as Dr. Marks was the **Director of the FDA's Center for Biologics Evaluation and Research (CBER)** which meant that he had overview responsibilities over all Biologics including those of *Active Immunization* (vaccines) and *Passive Immunization* (all exogenous immunoglobulins used to treat viruses and bacteria, toxins, and envenomations).

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The transcript of the attached video is as follows:

Anne Thompson: Controversial Health and Human Services Secretary Robert F Kennedy Jr.today slashing 10,000 jobs.

Kennedy: We're keenly focused on pairing away excess administrators while increasing the number of scientists and frontline health providers.

Anne Thompson: The cuts include 3500 employees at the FDA but not affecting inspectors or drug medical device or food reviewers. 2,400 at the CDC to focus on its core mission of preparing for and responding to epidemics. This on top of the 10,000 other workers gone in Elon musk's dose efforts--in all a 1/4 of the agency's workforce

You just can't eliminate 1/4 of the workforce and not have some effect on on agency operations

Anne Thompson: Katie Sandlin, one of those let go in the 1st wave says today's news compounds her disillusion.

Katie Sandlin: NIH is just not the place that I spent my entire career trying to reach anymore. At least from the outside looking in, that's how it feels.

Anne Thompson: Meanwhile, in West TX where there's a measles outbreak, it's vaccine skeptic Kennedy's words about alternative therapies that may have an impact.

Kennedy: And also cod liver oil which has high level high, high concentrations of vitamin A and vitamin D.

Anne Thompson: Doctors at Covenant Children's Hospital in Lubbock report a handful of cases--fewer than 10--involving liver damage caused by too much vitamin A. All the patients were unvaccinated. Dr. Anna Montana is a pediatrician in the area. Can cod liver oil prevent measles?

Dr. Montana: No ma'am.

Anne Thompson: Can it treat measles?

Dr. Montana: No ma'am. The only thing that prevents measles is vaccination.

Anne Thompson: Now Kennedy says he is giving the HHS a new charge to end what he calls a chronic illness epidemic by concentrating on safe wholesome food, clean water, and getting rid of environmental toxins. Lester…

Lester: Anne Thompson, thank you.

The Irish Times: Top vaccine official resigns from US FDA, citing Robert F Kennedy's 'misinformation and lies"—Dr Peter Marks steered the Food and Drug Administration's vaccine program during the coronavirus pandemic.—Dr Peter Marks said that he had been willing to address concerns raised by Robert F Kennedy (pictured) about vaccine safety and transparency, but was rebuffed. The Irish Times 2025 Mar 29 – 09:33 https://www.irishtimes.com/world/us/2025/03/29/top-vaccine-official-resigns-from-us-fda-citing-robert-f-kennedys-misinformation-and-lies/ from The New York Times: https://www.nytimes.com/2025/03/28/health/fda-vaccines-rfk-jr-peter-marks.html which is archived on the *Internet Archive*: https://web.archive.org/web/20250329013205/https://www.nytimes.com/2025/03/28/health/fda-vaccines-rfk-jr-peter-marks.html :

Jewett C, Stolber SG, Weiland Noah: Top F.D.A. Vaccine Official resigns, citing Kennedy's 'Misinformation and Lies' Dr. Peter Marks, a veteran of the agency, wrote that undermining confidence in vaccines is irresponsible and a danger to public health. March 28, 2025, 9:29 p.m. ET. The New York Times https://www.nytimes.com/2025/03/28/health/fda-vaccines-rfk-jr-peter-marks.html which is archived on the *Internet Archive*: https://web.archive.org/web/20250329013205/https://www.nytimes.com/2025/03/28/health/fda-vaccines-rfk-jr-peter-marks.html

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March 29, 2025: On Friday evening, 3/28/2025, it was announced that Peter Marks, M.D., PhD resigned from the FDA as the "top vaccine scientist." This statement of his being the "top vaccine scientist" was *palteringly* incorrect as Dr. Marks was the **Director of the FDA's Center for Biologics Evaluation and Research (CBER)** which meant that he had overview responsibilities regarding all Biologics including those of *Active Immunization* (vaccines) and *Passive Immunization* (all exogenous immunoglobulins used to treat viruses and bacteria, toxins, and envenomations).

Please note: My Letter (pages 11-74) to HHS Secretary Robert F. Kennedy was mailed on 03/22/2025 via USPS Priority Mail with tracking# 9405530109355121386196. It was reported on 3/29/2025 USPS tracking that it has yet to be delivered to Secretary Kennedy as is documented by the USPS tracking below. Such documentation implies that my recommendation that Secretary Kennedy speak with Dr. Marks (page 19) will arrive after he resigned or was fired. It is likely, though, that Secretary Kennedy was given a copy of my letter prior to Dr. Marks separation from the position of Director of the FDA's Center for Biologics Evaluation and Research (CBER) as I had attached a copy of my letter to Secretary Kennedy to an e-mail sent to Acting Surgeon General Denis Hinton, US PHS Rear Admiral, MS, RN, FAAN that was dated and timed: Monday, March 24, 2025 at 03:55 PM CDT **(page 345) which was thus delivered to the Office of the Surgeon General to the e-mail address:** surgeongeneral@hhs.gov **four days before Dr. Marks' resignation or firing as the Director of CBER.**

THIS IS EXTRMEMLY IMPORTANT as the *Passive Immunity* agent, GamaSTAN® S/D, a gamma globulin agent that was approved by the FDA in 1944; and GamaSTAN® S/D is still approved today in the treatment within six days of exposure to Hepatitis A and measles (Rubeola). In all the present discussions in the media today, nowhere is it stated that all those exposed to measles who are unvaccinated, under-vaccinated, or immunocompromised should be administered GamaSTAN® S/D or IVIG / Convalescent Plasma specific for measles (Rubeola).

THIS IS HOW THE PRESENT MEASLES OUTBREAKS SHOULD BE TREATED!

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Retired, Professor of Surgery, Saint Louis University School of Medicine
Retired, Physician and Surgeon, Veterans Health Administration,
U.S. Department of Veterans Affairs
NIH NIAID case file #12276
Home phone: 314-455-9482

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